April 8, 2003

APPENDIX A

Existing published and unpublished data were collected and scientifically evaluated to determine the best possible study or studies to be summarized for each required endpoint. In the spirit of this voluntary program, other data of equal or lesser quality are not summarized, but are listed as related references at the end of each appropriate section, with a statement to reflect the reason why these studies were not summarized.

1.0 Substance Information

CAS Number: 124-09-4

Chemical Name: 1,6-Hexanediamine

Structural Formula: $NH_2—CH-C-CH_2—C-CH-CH—NH_2$

Other Names:
1,6-Diaminohexane
1,6-Diamino-n-hexane
1,6-Hexylenediamine
1,6-Hexamethylenediamine
α-ω-Hexanediamine
Hexamethylenediamine
Hexylenediamine
HMD
HMDA
NCI-C61405

Exposure Limits: 1 ppm (8- and 12-hour TWA), vapor; 5 mg/m^3 (8- and 12-hour TWA), total dust: DuPont Acceptable Exposure Limit

TLV = 0.5 ppm; 2.3 mg/m^3 (8-hour TWA): ACGIH

TWA 1 mg/m^3; STEL 2 mg/m^3; Skin; January, 1993: OEL-Hungary

STEL 0.1 mg/m^3; January, 1993: OEL-Russia

1 ppm (8-hour TWA); 5 mg/m^3 (8-hour TWA), total particulate: WEEL

2.0 Physical/Chemical Properties

2.1 Melting Point (Freezing Point)

Value:	42 °C
Decomposition:	No Data
Sublimation:	No Data

Pressure:	No Data
Method:	No Data
GLP:	Unknown
Reference:	Budaveri, S. et al. (eds.) (1996). The Merck Index, 12th ed., p. 803, Merck & Co., Inc., Whitehouse Station, NJ.
Reliability:	Not assignable because limited study information was available. Handbook value.

Additional References for Melting Point:

BASF AG (1990). Safety Bulletin, Diamin H Extra (October) (cited in BASF (1991). AIDA Basic Data Set).

DuPont (2001). Material Safety Data Sheet No. DU008214 (May 17).

SIDS Dossier for 1,6-Hexanediamine (http://www1.oecd.org/ehs/sidstable/index.htm accessed on February 19, 2002).

BASF AG (1994). Sicherheitsdatenblatt Diamin H extra (07.03.1994) (cited in IUCLID (2000). IUCLID Dataset, "Hexamethylenediamine" (February 18)).

Weast, R. C. et al. (1987). CRC Handbook of Chemistry and Physics, 68th ed., CRC Press Inc., Boca Raton, FL.

2.2 Boiling Point

Value:	205 °C
Decomposition:	No Data
Pressure:	No Data
Method:	No Data
GLP:	Unknown
Reference:	Budaveri, S. et al. (eds.) (1996). The Merck Index, 12th ed., p. 803, Merck & Co., Inc., Whitehouse Station, NJ.
Reliability:	Not assignable because limited study information was available. Handbook value.

Additional References for Boiling Point:

DuPont (2001). Material Safety Data Sheet No. DU008214 (May 17).

SIDS Dossier for 1,6-Hexanediamine (http://www1.oecd.org/ehs/sidstable/index.htm accessed on February 19, 2002).

BASF AG (1994). Sicherheitsdatenblatt Diamin H extra (07.03.1994) (cited in IUCLID (2000). IUCLID Dataset, "Hexamethylenediamine" (February 18)).

BASF AG (1990). Safety Bulletin, Diamin H Extra (October) (cited in BASF (1991). AIDA Basic Data Set).

BASF AG (1987). Data Bulletin (December) (cited in BASF (1991). AIDA Basic Data Set).

Grasselli, J. G. and W. M. Ritchey (1975). Chemical Rubber Company Atlas of Spectral Data and Physical Constants for Organic Compounds, 2nd ed., CRC Press, Inc., Cleveland, Ohio (NISC/IS-0006803).

2.3 Density

Value:	0.833 g/cm^3
Temperature:	60ºC
Method:	No Data
GLP:	Unknown
Results:	No additional data.
Reference:	BASF AG (1994). Sicherheitsdatenblatt Diamin H extra (07.03.1994) (cited in IUCLID (2000). IUCLID Dataset, "Hexamethylenediamine" (February 18)).
Reliability:	Not assignable because limited study information was available.

Additional References for Density:

Monsanto Co. (1984). TSCA Fiche OTS0001068.

U.S. Coast Guard, Department of Transportation (1978). CHRIS – Hazardous Chemical Data, Manual Two, U.S. Government Printing Office, Washington, DC (HSDB/189).

Clayton, G. D. and F. E. Clayton (1981-1982). Patty's Industrial Hygiene and Toxicology, Volume 2A, 2B, 2C: Toxicology, 3rd ed., p. 3140, John Wiley Sons, New York (HSDB/189).

DuPont (2001). Material Safety Data Sheet No. DU008214 (May 17).

BASF AG (1990). Safety Bulletin, Diamin H Extra (October) (cited in BASF (1991). AIDA Basic Data Set).

BASF AG (1987). Data Bulletin (December) (cited in BASF (1991). AIDA Basic Data Set).

2.4 Vapor Pressure

Value:	3 mm Hg (100%)

Temperature:	60 °C
Decomposition:	No Data
Method:	No Data
GLP:	Unknown
Reference:	DuPont (2001). Material Safety Data Sheet No. DU008214 (May 17).
Reliability:	Not assignable because limited study information was available.

Additional References for Vapor Pressure:

Yaws, C. L. (1994). Handbook of Vapor Pressure, Vol. 2, C5 to C7 Compounds, Gulf Publ. Co., Houston, TX (HSDB/187).

SIDS Dossier for 1,6-Hexanediamine (http://www1.oecd.org/ehs/sidstable/index.htm accessed on February 19, 2002).

BASF AG (1994). Sicherheitsdatenblatt Diamin H extra (07.03.1994) (cited in IUCLID (2000). IUCLID Dataset, "Hexamethylenediamine" (February 18)).

BASF AG (1990). Safety Bulletin, Diamin H Extra (October) (cited in BASF (1991). AIDA Basic Data Set).

2.5 Partition Coefficient (log Kow)

Value:	0.35 (Estimated)
Temperature:	No Data
Method:	Modeled. KOWWIN, v. 1.66, module of EPIWIN 3.05 (Syracuse Research Corporation). KOWWIN uses "fragment constant" methodologies to predict log P. In a "fragment constant" method, a structure is divided into fragments (atom or larger functional groups), and coefficient values of each fragment or group are summed together to yield the log P estimate.
GLP:	Not Applicable
Reference:	Meylan ,W. M. and P. H. Howard (1995). J. Pharm. Sci., 84:83-92 (HSDB/187).
Reliability:	Not assignable because limited study information was available.

Additional References for Partition Coefficient (log Kow):

SIDS Dossier for 1,6-Hexanediamine (http://www1.oecd.org/ehs/sidstable/index.htm accessed on February 19, 2002).

BASF AG (1994). Sicherheitsdatenblatt Diamin H extra (07.03.1994) (cited in

IUCLID (2000). IUCLID Dataset, "Hexamethylenediamine" (February 18)).

BASF AG (n.d.). Analytical Laboratory, Unpublished Investigation (BRU 88.78) (cited in IUCLID (2000). IUCLID Dataset, "Hexamethylenediamine" (February 18)).

Leo, A. J. (1978). Report on the Calculation of Octanol/Water Log P Values for Structures in EPA Files (NISC/IS-0006805 and 0006806).

Schill, G. (1965). Acta Pharma. Suecica, 2:13 (NISC/IS-0006807).

2.6 Water Solubility

Value:	960 g/100 g H_20
Temperature:	30 °C
pH/pKa:	Estimated pKa: 10.2
Method:	No Data pKa – SPARC on-line calculator, University of Georgia
GLP:	Unknown
Reference:	DuPont Co. (1964). Unpublished Data, "Water Solubility Test" pKa - http://ibmlc2.chem.uga.edu/sparc/index.cfm
Reliability:	Not assignable because limited study information was available.

Additional References for Water Solubility:

Budavari, S. (ed.) (1996). The Merck Index – An Encyclopedia of Chemicals, Drugs, and Biologicals, p. 802, Merck and Co., Inc., Whitehouse Station, NJ (HSDB/189).

Yalkowsky, S. H. and R. M. Dannenfelser (1992). The AQUASOL DATABASE of Aqueous Solubility, 5th ed., Univ. Az., College of Pharmacy, Tucson, AZ (HSDB/189).

SIDS Dossier for 1,6-Hexanediamine (http://www1.oecd.org/ehs/sidstable/index.htm accessed on February 19, 2002).

BASF AG (n.d.) Internal test (cited in BASF (1991). AIDA Basic Data Set).

BASF AG (1994). Sicherheitsdatenblatt Diamin H extra (07.03.1994) (cited in IUCLID (2000). IUCLID Dataset, "Hexamethylenediamine" (February 18)).

Hann, R. W., Jr. and P. A. Jensen (1977). NTIS-PB-285946, Texas A&M Univ., College Station Environmental Engineering Div. (NISC/EF-0011837).

2.7 Flash Point

Value:	85°C (100% conc.); 94-116°C (70-90% conc.)
Method:	COC
GLP:	Unknown
Reference:	DuPont (2001). Material Safety Data Sheet No. DU008214 (May 17).
Reliability:	Not assignable because limited study information was available.

Additional References for Flash Point:

U.S. Coast Guard, Department of Transportation (1978). CHRIS – Hazardous Chemical Data, Manual Two, U.S. Government Printing Office, Washington, DC (HSDB/189).

BASF AG (1994). Sicherheitsdatenblatt Diamin H extra (07.03.1994) (cited in IUCLID (2000). IUCLID Dataset, "Hexamethylenediamine" (February 18)).

2.8 Flammability

Results:	0.9-4.1%; Autoignition = 390-420°C
Method:	No Data
GLP:	Unknown
Reference:	DuPont (2001). Material Safety Data Sheet No. DU008214 (May 17).
Reliability:	Not assignable because limited study information was available.

Additional References for Flammability:

U.S. Coast Guard, Department of Transportation (1978). CHRIS – Hazardous Chemical Data, Manual Two, U.S. Government Printing Office, Washington, DC (HSDB/189).

SIDS Dossier for 1,6-Hexanediamine (http://www1.oecd.org/ehs/sidstable/index.htm accessed on February 19, 2002).

BASF AG (1994). Sicherheitsdatenblatt Diamin H extra (07.03.1994) (cited in IUCLID (2000). IUCLID Dataset, "Hexamethylenediamine" (February 18)).

3.0 Environmental Fate

3.1 Photodegradation

Concentration:	Not Applicable
Temperature:	25° C
Direct Photolysis:	Not Applicable
Indirect Photolysis:	$t_{1/2}$ = 6 hours
Breakdown Products:	Not Determined
Method:	According to a model of gas/particle partitioning of semivolatile organic compounds in the atmosphere (Bidleman, 1988), hexamethylenediamine, which has an extrapolated vapor pressure of 0.12 mm Hg at 25°C (Yaws, 1994; SRC, n.d.), is expected to exist solely as a vapor in the ambient atmosphere. The rate constant for the vapor-phase reaction of hexamethylenediamine with photochemically-produced hydroxyl radicals has been estimated as $6.9x10^{-11}$ cm^3/molecule-sec at 25°C (SRC, n.d.) using a structure estimation method (Meylan and Howard, 1993; SRC, n.d.). This corresponds to an atmospheric half-life of about 6 hours at an atmospheric concentration of $5x10^5$ hydroxyl radicals per cm^3 (Meylan and Howard, 1993; SRC, n.d.). An experimental pKa value of 11 (Perrin, 1972), indicates that hexamethylenediamine will not dissociate significantly at environmentally important pH values (SRC, n.d.). Hexamethylenediamine is not expected to undergo hydrolysis or direct photolysis in the environment due to the lack of functional groups to hydrolyze or absorb UV radiation at environmentally significant wavelengths (SRC, n.d.).
GLP:	Not Applicable
Reference:	Bidleman, T. F. (1988). Environ. Sci. Technol., 22:361-367 (HSDB/187). Yaws, C. L. (1994). Handbook of Vapor Pressure, Vol 2, C5 to C7 Compounds, Gulf Publ. Co., Houston, TX (HSDB/187). Meylan, W. M. and P. H. Howard (1993). Chemosphere, 26:2293-99 (HSDB/187). Perrin, D. D. (1972). Dissociation Constants of Organic Bases in Aqueous Solution, IUPAC Chemical Series: Supplement, Buttersworth, London (HSDB/187).

	SRC (n.d.). Syracuse Research Corporation (HSDB/187).
Reliability:	Estimated value based on accepted model.

Additional References for Photodegradation:

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

SIDS Dossier for 1,6-Hexanediamine (http://www1.oecd.org/ehs/sidstable/index.htm accessed on February 19, 2002).

Meylan, W. and P. Howard (1993). Atmospheric Oxidation Program Version 1.5, Syracuse Research Corporation, New York (cited in IUCLID (2000). IUCLID Dataset, "Hexamethylenediamine" (February 18)).

3.2 Stability in Water

Concentration:	Not Applicable
Half-life:	Estimated greater than 1 year.
% Hydrolyzed:	Not Applicable
Method:	The stability of this material in water is estimated based on established chemical principles. Amines are considered resistant to hydrolysis by Harris (Harris, J. C. in Lyman W, et al. (1990). Handbook of Chemical Property Estimation Methods, p. 7-6, American Chemical Society, Washington D.C.). This indicates a hydrolytic half-life of greater than one year.
GLP:	Not Applicable
Reference:	Lyman, W. J. et al. (1990). Handbook of Chemical Property Estimation Methods, pp. 4-9, 5-4, 5-10, 15-1 to 15-29, Amer. Chem. Soc., Washington, DC.
Reliability:	Estimated value based on chemical principles.

Additional Reference for Stability in Water:

Data from this additional source support the study results summarized above. This study was not chosen for detailed summarization because the data were not substantially additive to the database.

SIDS Dossier for 1,6-Hexanediamine (http://www1.oecd.org/ehs/sidstable/index.htm accessed on February 19, 2002).

3.3 Transport (Fugacity)

Media:	Air, Water, Soil, and Sediments	
Distributions:	Air:	0.016%
	Water:	38%
	Soil:	61.9%
	Sediments:	0.71%
Half-life:	Air:	5.58 h
	Water:	360 h
	Soil:	720 h
	Sediments:	3240 h
Adsorption Coefficient:	Not Applicable	
Desorption:	Not Applicable	
Volatility:	Not Applicable	
Method:	Calculated according to Mackay, Level III, Syracuse Research Corporation EPIWIN v3.05. Emissions (1000 kg/hr) to air, water, and soil compartments using standard EPA model defaults.	
	Data Used: Molecular Weight: 116.21 Henry's Law Constant: 7.05e-10 atm-m^3/mole (HENRYWIN Program) Vapor Pressure: 0.183 mm Hg Log Kow: 0.35 Soil Koc: 0.918	
GLP:	Not Applicable	
Reference:	Syracuse Research Corporation EPIWIN v3.05 contains a Level III fugacity model. The methodology and programming approach were developed by Dr. Donald MacKay and coworkers and are detailed in: Mackay, D. (1991). Multimedia Environmental Models: The Fugacity Approach, pp. 67-183, Lewis Publishers, CRC Press. Mackay, D. et al. (1996). Environ. Toxicol. Chem., 15(9):1618-1626. Mackay, D. et al. (1996). Environ. Toxicol. Chem., 15(9):1627-1637.	
Reliability:	Estimated value based on accepted model.	

Additional References for Transport (Fugacity): None Found.

3.4 Biodegradation

Value:	Using a standard BOD dilution technique and an activated sludge inoculum, a theoretical BOD of 56% was observed during a 14-day incubation period (Chemicals Inspection and Testing Institute, 1992). Using standard BOD dilution techniques and activated sludge inocula, theoretical BOD values of 41% to 56% were observed during a 14-day incubation period following a 6-day acclimation period (Urano and Kato, 1986). Based on 14-day BOD data, hexamethylenediamine is considered biodegradable. Greater than 30% was degraded after 14 days in an Original MITI Test (C-5/98/JAP) (Sasaki, 1978). Following a 3-day acclimation period, 90% biodegradation of hexamethylenediamine in an activated sludge inoculum was observed during a 6-day incubation period, with an average COD of 26% per day (HSDB/187). Degradation rates of 4% and 10% were observed for hexamethylenediamine (50 ppm) incubated in water from the Mino River, Japan and seawater off the coast of Japan over a 3-day incubation period (Kondo et al., 1988). A theoretical oxygen demand between 20 and 60% was observed for hexamethylenediamine in a Warburg apparatus during a 5-day incubation period (Wotzka et al., 1993).
Breakdown Products:	No Data
Method:	See above
GLP:	Unknown
Reference:	Chemicals Inspection and Testing Institute (1992). Japan Chemical Industry Ecology - Toxicology and Information Center, ISBN 4-89074-101-1 (HSDB/187). Urano, K. and Z. Kato (1986). J. Haz. Mat., 13:147-59 (HSDB/187). Sasaki, S. in Aquatic Pollutants: Transformation and Biological Effects, Hutzinger, O. et al. (eds.) (1978). Pergamon Press, Oxford (HSDB/187 and cited in IUCLID

(2000). IUCLID Dataset, "Hexamethylenediamine" (February 18)).

Kondo, M. et al. (1988). Eisei Kagaku, 34:188-95 (HSDB/187).

Wotzka, J. et al. (1993). Dtsc. Gewaesserkd. Mitt., 37:106-113 (HSDB/187).

Reliability: High because a scientifically defensible or guideline methods were used, which yielded results consistent with other reported studies.

Additional References for Biodegradation:

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

Bruk, E. S. et al. (1965). Sanit. Okhr. Vodoemov Zagryaz. Prom. Stochnymi Vodami, (7):69-83 (CA66:49145c).

Zahn, R. and W. Huber (1975). W. Tenside Detergents, 12:226-270 (cited in SIDS Dossier for 1,6-Hexanediamine (http://www1.oecd.org/ehs/sidstable/index.htm accessed on February 19, 2002) and cited in IUCLID (2000). IUCLID Dataset, "Hexamethylenediamine" (February 18)).

Kuhit (1989). Test Procedure, 2(113):257 (cited in SIDS Dossier for 1,6-Hexanediamine (http://www1.oecd.org/ehs/sidstable/index.htm accessed on February 19, 2002)).

Zahn, R. and H. Wellens (1980). H. Zeitschrift fuer Wasser und Abwasser Forshung, 13(1):1-7 (cited in SIDS Dossier for 1,6-Hexanediamine (http://www1.oecd.org/ehs/sidstable/index.htm accessed on February 19, 2002) and cited in IUCLID (2000). IUCLID Dataset, "Hexamethylenediamine" (February 18)).

BASF AG (1974). Unpublished Report, June 14 (cited in SIDS Dossier for 1,6-Hexanediamine (http://www1.oecd.org/ehs/sidstable/index.htm accessed on February 19, 2002) and cited in IUCLID (2000). IUCLID Dataset, "Hexamethylenediamine" (February 18)).

BASF AG (n.d.). Safety Bulletin (cited in SIDS Dossier for 1,6-Hexanediamine (http://www1.oecd.org/ehs/sidstable/index.htm accessed on February 19, 2002) and cited in IUCLID (2000). IUCLID Dataset, "Hexamethylenediamine" (February 18)).

Versuchsprotokoll Institut Kuhlmann (n.d.). 2-113-257/89 (cited in IUCLID (2000). IUCLID Dataset, "Hexamethylenediamine" (February 18)).

Kawasaki, M. (1980). Ecotox. Environ. Saf., 4:444-454 (cited in IUCLID (2000). IUCLID Dataset, "Hexamethylenediamine" (February 18)).

Grula, M. M. and E. A. Grula (1976). ERDA Energy Res. Abst. (NISC/BD-0005666).

Yamaguchi, N. et al. (1997). Japan. J. Toxicol. Environ. Health, 43(4):209-214 (BIOSIS/97/32637).

3.5 Bioconcentration

Value:	BCF = 1
Method:	An estimated BCF value of 1 was calculated for hexamethylenediamine (SRC, n.d.), using an estimated log Kow of 0.35 (Meylan and Howard, 1995; SRC, n.d.) and a recommended regression-derived equation (Lyman et al., 1990). According to a classification scheme (Franke et al., 1994), this BCF value suggests that bioconcentration in aquatic organisms is low (SRC, n.d.).
GLP:	Not Applicable
Reference:	Meylan ,W. M. and P. H. Howard (1995). J. Pharm. Sci., 84:83-92 (HSDB/187). Lyman, W. J. et al. (1990). Handbook of Chemical Property Estimation Methods, pp. 4-9, 5-4, 5-10, 15-1 to 15-29, Amer. Chem. Soc., Washington, DC (HSDB/187). Franke, C. et al. (1994). Chemosphere, 29:1501-14 (HSDB/187). SRC (n.d.). Syracuse Research Corporation (HSDB/187).
Reliability:	Estimated value based on accepted model.

Additional Reference for Bioconcentration:

Data from this additional source support the study results summarized above. This source was not chosen for detailed summarization because the data were not substantially additive to the database.

SIDS Dossier for 1,6-Hexanediamine (http://www1.oecd.org/ehs/sidstable/index.htm accessed on February 19, 2002).

4.0 Ecotoxicity

4.1 Acute Toxicity to Fish

Type:	**96-hour LC_{50}**
Species:	Fathead minnow, *Pimephales promelas*
Value:	1435 mg/L (95% confidence limits, 1542-1953 mg/L)
Method:	No specific test guideline was reported; however, a scientifically defensible approach was used to conduct the study.

The test material was prepared as a 600 g/L stock solution in laboratory well water. Because of the caustic nature of the test material, the pH of the stock solution was adjusted to 8.0-8.5 with a 10% solution of HCl. Approximate volumes of the stock solution were then placed into 5-L glass aquaria and diluted with additional laboratory well water to yield the desired nominal exposure concentrations in 4-L final volumes. Two identical vessels, each containing only laboratory well water were designated as the H_2O controls.

Stability of the test and control materials in laboratory well water was not determined.

Ten juvenile, unsexed fathead minnows with a 2.85 cm mean standard length (range 2.2 to 3.8 cm) and a 0.29 g mean wet weight (range 0.11 to 0.64 g) were randomly placed in each vessel. Fish were not fed for 48 hours prior to nor during the exposure. The test solutions were not aerated, and temperature was maintained at 22ºC. Photoperiod was maintained at 16 hours light and 8 hours dark. Mortality counts and observations were made every 24 hours during the 96-hour exposure period. Concentrations of 750, 1000, 1800, 2360, 3150, 4200, 5600, 7500, and 10,000 mg/L were used in the study.

Dissolved oxygen and pH were measured in the control, low (750 mg/L), medium (3150 mg/L), and high (10,000 mg/L) test concentrations at the beginning of the test and at 24-hour intervals during the 96-hour exposure period. Total alkalinity, hardness (EDTA), and conductivity were measured at the beginning of the test in the control.

The 96-hour LC_{50} and confidence limits were calculated by the Trimmed Spearman-Karber technique.

GLP: No

Test Substance: 1,6-Hexanediamine, purity 84.6%

Results: Dissolved oxygen levels ranged from 6.7–8.8, 5.9–8.9, 7.0-8.9, and 8.1-8.9 in the control, low, medium, and high concentrations, respectively. pH ranged from 7.6-7.7, 8.2-8.4, 8.0-8.5, and 8.2-8.5 in the control, low, medium, and high concentrations, respectively. Total alkalinity at test start was 81 mg/L $CaCO_3$ in the control. EDTA hardness in the control at test start was 79 mg/L as $CaCO_3$. Conductivity in the control at test start was 162 µmhos/cm.

The observed mortality at 96-hours is presented in the table below.

Nominal Test Concentration (mg/L)	% Mortality 96-hour Replicate A	% Mortality 96-hour Replicate B
0	0	0
750	0	0
1000	0	0
1800	70	100
2360	60	90
3150	90	70
4200	100	70
5600	100	90
7500	100	100
10,000	100	100

At nominal concentrations of 4200 mg/L and greater, some fish exhibited clinical signs including erratic swimming, swimming at the surface, partial loss of equilibrium, and laying on the bottom.

Reference: DuPont Co. (1985). Unpublished Data, Haskell Laboratory Report No. HL-439-85, "Static Acute 96-Hour LC_{50} of 1,6-Hexanediamine to the Fathead Minnow, *Pimephales promelas*" (October 3).

Reliability: Medium because a suboptimal study design (nominal test concentrations) was used for testing.

Type: **96-hour LC_{50}**

Species: Freshwater fish

Value: 364 mg/L

Method: Modeled, ECOSAR (using log Kow of 0.35)

GLP: Not Applicable

Test Substance: 1,6-Hexanediamine

Results: No additional data.

Reference: Meylan, W. M. and P. H. Howard (1999). User's Guide for

the ECOSAR Class Program, Version 0.993 (Mar 99), prepared for J. Vincent Nabholz and Gordon Cas, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics, Washington, DC, prepared by Syracuse Research Corp., Environmental Science Center, Syracuse, NY 13210 (submitted for publication).

Reliability: Estimated value based on accepted model.

Additional References for Acute Toxicity to Fish:

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

BASF AG (1992). Abt. Toxikolgie, unpublished investigation (90/733) 03.01.92 (cited in IUCLID (2000). IUCLID Dataset, "Hexamethylenediamine" (February 18)).

Scheier, A. (1965). Academy of Natural Sciences of Philadelphia, Department of Limnology.

DuPont Co. (1969). Unpublished Data, Haskell Laboratory Report No. HL-40-69, "Hexamethylene-diamine – Evaluation of Acute LC_{50} for Bluegill Sunfish" (February 19) (cited in TSCA Fiche OTS0000931).

BASF AG (n.d.). Safety Bulletin (cited in SIDS Dossier for 1,6-Hexanediamine (http://www1.oecd.org/ehs/sidstable/index.htm accessed on February 19, 2002)).

4.2 Acute Toxicity to Invertebrates

Type: **48-hour EC_{50}**
Species: *Daphnia magna*
Value: 23.4 mg/L (95% confidence limits, 21.1-25.9 mg/L)
Method: No specific test guideline was reported; however, a scientifically defensible approach was used to conduct the study.

The test material was prepared as a 5000 mg/L stock solution in filtered distilled water adjusted to pH 8.5 with a 10% solution of HCl and diluted with filtered laboratory water to yield the desired concentrations. After mixing, 200 mL aliquots of each concentration were introduced into two separate 250 mL glass exposure vessels. Two identical vessels, each containing only laboratory water were designated as the dilution water controls.

Stability of the test and control materials in dilution water was not determined.

Ten daphnids, < 24 hours old, were placed in each vessel. Food was not provided during the test. The test solutions were not aerated, and temperature was maintained between 20.0-20.1ºC. Photoperiod was maintained at 16 hours light and 8 hours dark. Immobility counts and observations were made at 24 and 48 hours after the exposure was initiated. Concentrations of 10, 15, 18, 24, 32, 42, 56, 75, and 100 mg/L were used in the study. Concentrations were nominal; no analytical determinations were conducted. As the stock solution was pH adjusted to 8.5, this is considered a pH-adjusted test.

Dissolved oxygen and pH were measured in the control, low (10 mg/L), medium (32 mg/L), and high (100 mg/L) test concentrations at the beginning and end of period. Total alkalinity, hardness (EDTA), and conductivity were measured at the beginning of the test in the control.

The 48-hour EC_{50} and confidence limits were calculated by probit analysis.

GLP: No

Test Substance: 1,6-Hexanediamine, purity 84.6%

Results: Dissolved oxygen levels ranged from 67.0–8.6, 7.5–8.7, 7.6-8.7, and 7.6-8.7 in the control, low, medium, and high concentrations, respectively. pH ranged from 8.0-8.5, 7.9-8.2, 8.0-8.2, and 7.9-8.2 in the control, low, medium, and high concentrations, respectively. Total alkalinity at test start was 96 mg/L $CaCO_3$ in the control. EDTA hardness in the control at test start was 83 mg/L as $CaCO_3$. Conductivity in the control at test start was 180 µmhos/cm.

The observed immobility at 48-hours is presented in the table below.

Nominal Test Concentration (mg/L)	% Immobility 48-hour Replicate A	% Immobility 48-hour Replicate B
0	0	0
10	0	0
15	10	0
18	0	40
24	50	40
32	90	80

42	100	100
56	100	100
75	100	100
100	100	100

Reference: DuPont Co. (1985). Unpublished Data, Haskell Laboratory Report No. HL-303-85, "Static Acute 48-Hour EC_{50} of 1,6-Hexanediamine to *Daphnia magna*" (June 10).
Reliability: Medium because a suboptimal study design (nominal concentrations) was used for testing.

Type: **48-hour EC_{50}**
Species: Daphnid
Value: 21.8 mg/L
Method: Modeled, ECOSAR (using log Kow of 0.35)
GLP: Not Applicable
Test Substance: 1,6-Hexanediamine
Results: No additional data.
Reference: Meylan, W. M. and P. H. Howard (1999). User's Guide for the ECOSAR Class Program, Version 0.993 (Mar 99), prepared for J. Vincent Nabholz and Gordon Cas, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics, Washington, DC, prepared by Syracuse Research Corp., Environmental Science Center, Syracuse, NY 13210 (submitted for publication).
Reliability: Estimated value based on accepted model.

Additional References for Acute Toxicity to Invertebrates:

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

Roi, A. A. and S. V. Garbara (1978). Gig. Sanit., (11):110 (CA90:17271v).

Adema, D. M. M. (1982). Tests and desk studies carried out by MT-TNO during 1980-1981 for Annex II of Marpol 1973, Delft, TNO, 1982, Rep. No. CL82/14 (cited in IUCLID (2000). IUCLID Dataset, "Hexamethylenediamine" (February 18)).

Monsanto Co. (1984). Unpublished Report No. ESC-EAG-84-8, "Acute Toxicity of Hexamethylenediamine to *Daphnia Magna*" (April 30).

4.3 Acute Toxicity to Aquatic Plants

Type: **96-hour EC_{50}**

Species:	Algae, *Selenastrum capricornutum*
Value:	14.8 mg/L (95% confidence limits, 14.2-15.5 mg/L)
Method:	The procedure used in the test were based on the recommendations of the following guideline: OECD 201. The test was conducted at a target temperature of 22-25ºC with 0, 10, 15, 25, 40, 60, and 100 mg/L of the test substance. A 100 mg/L stock solution was formulated in sterile enriched media and the final volume adjusted to 1 L. Algae was distributed among 3 replicates of each treatment at the rate of approximately 10,000 cells/mL. The test was performed in 250 mL glass Erlenmeyer flasks that contained 100 mL of test solution. Test vessels were randomly arranged on a rotary shaker in an incubator during the test. A 24 hour light and 0 hour dark photoperiod was maintained. The number of algal cells/mL in each test vessel and the occurrence of relative size differences, unusual cell shapes, colors, flocculations, adherence of cells to test containers, or aggregation of cells was determined visually by means of direct microscopic examination with a haemocytometer. Cell counts were made and recorded daily during the 96-hour test. Temperature of the incubator was determined daily and pH of the incubator was determined at the beginning and end of the test Results of the toxicity test were interpreted by standard statistical techniques. The binomial/nonlinear interpolation method was used to calculate the 24- and 48-hour EC_{50}s and the probit method was used to determine 72- and 96-hour EC_{10}, EC_{50}, and EC_{90} values and the slope of the dose response curve. The no observed concentration was determined by Dunnett's test, which includes an analysis of variance (ANOVA), using the mean number of algal cells per mL in each test vessel at 96 hours. Nominal concentrations were used for all calculations.
GLP:	Yes
Test Substance:	1,6-Hexanediamine, purity 85%
Results:	Water quality throughout the test was within acceptable limits. The temperature of the incubator ranged from 24.4-25.0ºC throughout the test period. The pH ranged from 7.5-9.7, 9.5-9.7, 8.6-9.9, 8.1-10.2, 8.0-10.4, 8.1-10.6, and 8.4-10.8 for the 0, 10, 15, 25, 40, 60, and 100 mg/L concentrations, respectively. The 24-hour EC_{50} = 17.0 mg/L.

The 48-hour EC_{50} = 17.6 mg/L.

The 72-hour EC_{10} = 11.3 mg/L.
The 72-hour EC_{50} = 15.0 mg/L.
The 72-hour EC_{90} = 19.9 mg/L.

The 96-hour NOEC = 10 mg/L.
The 96-hour LOEC = 15 mg/L.

The 96-hour EC_{10} = 11.3 mg/L.
The 96-hour EC_{50} = 14.8 mg/L.
The 96-hour EC_{90} = 19.4 mg/L.

No effects (size differences, unusual cell shapes, colors, flocculations, adherence of cells to test containers, or aggregation of cells) were noted.

Reference: DuPont Co. (1993). Unpublished Data, Haskell Laboratory Report No. HL-167-93, "Acute Toxicity to the Freshwater Alga, *Selenastrum capricornutum*" (March 30).

Reliability: Medium because a suboptimal study design (nominal concentrations) was used for testing.

Type: **96-hour EC_{50}**
Species: Green algae
Value: 23.2 mg/L
Method: Modeled, ECOSAR (using log Kow of 0.35)
GLP: Not Applicable
Test Substance: 1,6-Hexanediamine
Results: No additional data.
Reference: Meylan, W. M. and P. H. Howard (1999). User's Guide for the ECOSAR Class Program, Version 0.993 (Mar 99), prepared for J. Vincent Nabholz and Gordon Cas, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics, Washington, DC, prepared by Syracuse Research Corp., Environmental Science Center, Syracuse, NY 13210 (submitted for publication).
Reliability: Estimated value based on accepted model.

Additional References for Acute Toxicity to Aquatic Plants: None Found.

5.0 Mammalian Toxicity

5.1 Acute Toxicity

Type: **Oral LD_{50}**

Species/Strain: Rat/Crl:CD®

Value: 792 mg/kg (fasted rat) (95% confidence limits, 704-896 mg/kg)
1127 mg/kg (non-fasted rat) (95% confidence limits, 594-1344 mg/kg)

Method: No specific test guideline was reported; however, a scientifically defensible approach was used to conduct the study.

The test material, as a suspension in corn oil, was administered by intragastric intubation in single doses to 9 groups of 10 non-fasted (800, 1000, 1100, 1200, 1250, 1300, 1400, 1600, and 2000 mg/kg) and 4 groups of fasted (500, 700, 800, 1000 mg/kg) young adult male rats. The surviving rats were weighed and observed during a 14- or 16-day recovery period and then sacrificed. The LD_{50} value was calculated from the mortality data using the method of D. J. Finney.

GLP: No

Test Substance: 1,6-Hexanediamine, purity 90.54%

Results: Mortality ratios of 0/10, 2/10, 7/10, and 8/10 were observed for the 500, 700, 800, and 1000 mg/kg fasted dose groups, respectively. The following clinical observations were observed in the fasted rats:

Dose (mg/kg)	**Observation**
500	Weakness, stained and wet perineal area, stained face, congestion, and slight weight loss.
700	Weakness, stained and wet perineal area, stained face, diarrhea, congestion, alopecia, and slight weight loss. All deaths occurred within 1 day after dosing.
800	Weakness, lacrimation, stained and/or wet perineal area, stained face, pallor, diarrhea, chromodacryorrhea, and slight to moderate weight loss. All deaths occurred within 2 days after dosing.
1000	Weakness, stained and/or wet perineal area, stained face, and moderate weight loss. All deaths occurred within 1 day after dosing.

Mortality ratios of 0/10, 5/10, 5/10, 0/10, 9/10, 9/10, 9/10, 10/10, and 10/10 were observed for the 800, 1000, 1100,

1200, 1250, 1300, 1400, 1600, and 2000 mg/kg non-fasted dose groups, respectively. The following clinical observations were observed in the non-fasted rats:

Dose (mg/kg)	Observation
800	Weakness, stained and/or weight perineal area, stained face, congestion, and slight to moderate weight loss.
1000	Weakness, stained and/or weight perineal area, stained face, and moderate weight loss. All deaths occurred within 1 day of dosing.
1100	Weakness, stained and/or weight perineal area, diarrhea, lacrimation, stained face, and slight to moderate weight loss. All deaths occurred within 2 days of dosing.
1200	Stained perineal area and slight weight loss.
1250	Weakness, stained and/or wet perineal area, stained face, and slight weight loss. All deaths occurred within 1 day after dosing.
1300	Stained and/or wet perineal area, stained face, diarrhea, weakness, and severe weight loss. All deaths occurred within 2 days after dosing.
1400	Weakness, diarrhea, stained and wet perineal area, chromodacryorrhea, stained face, and severe weight loss. All deaths occurred within 2 days after dosing.
1600	Weakness. All deaths occurred within 1 day after dosing.
2000	Salivation. All deaths occurred within 1 day after dosing.

Reference: DuPont Co. (1981). Unpublished Report No. 111-81, "Oral LD_{50} Test in Fasted and Non-Fasted Rats" (February 23) (also cited in Dashiell, O. L. and G. L. Kennedy, Jr. (1984). J. Appl. Toxicol., 4(6):320-325 and cited in TSCA Fiche OTS0000931).

Reliability: High because a scientifically defensible or guideline method was used.

Additional References for Acute Oral Toxicity:

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

Monsanto Co. (1968). Unpublished report, "Toxicological Investigation of CP 54121", Younger Laboratories, Monsanto Project Number Y-68-20 (February 15).

DuPont Co. (1948). Unpublished Data, Haskell Laboratory Report No. HL-8-48, "Acute Toxicity Tests with Hexamethylenediamine" (February 3) (cited in TSCA Fiche OTS0000931).

Kennedy, G. L., Jr. et al. (1986). J. Appl. Toxicol., 6(3):145-148.

Dieke, S. H. et al. (1947). J. Pharmacol. Exp. Ther., 90:260-270 (CA41:6662g).

Back, K. C. et al. (1976). Toxicological Testing of Selected Hazardous Materials for Transportation Purposes, NTIS AD-A059077 (OHMTADS).

Vernot, E. H. et al. (1977). Toxicol. Appl. Pharmacol., 42(2):417-423 (CA88:84173m).

Johannsen, F. R. and G. J. Levinskas (1987). J. Appl. Toxicol., 7(4):259-263.

Procter & Gamble Co. (1977). "The Acute Toxicity (LD_{50}) of 1,6-Hexanediamine" (3/8/77) (cited in TSCA Fiche No. OTS0542112).

BASF AG (1959). Depart. Toxicology, Unpublished investigation VII/258, 20.02.1959 (cited in IUCLID (2000). IUCLID Dataset, "Hexamethylenediamine" (February 18)).

Standard Oil Co. (n.d.). (cited in TSCA Fiche No. OTS0206578).

BASF AG (1986). Dept. Toxicology, Unpublished investigation 85/370 (cited in BASF (1991). AIDA Basic Data Set).

BASF AG (1986). Dept. Toxicology, Unpublished investigation 85/372 (cited in BASF (1991). AIDA Basic Data Set).

BASF AG (1986). Dept. Toxicology, Unpublished investigation 85/371 (cited in BASF (1991). AIDA Basic Data Set).

Type:	**Inhalation LC_{50}**
Species/Strain:	Rats/Charles River
Exposure Time:	4 hours
Value:	> 0.95 mg/L

Method:	No specific test guideline was reported; however, a scientifically defensible approach was used to conduct the study. Five male and 5 female young adult rats were exposed to 0.95 mg/L of the test substance via inhalation (attempted vapor, probably an aerosol-vapor mixture). A heated vapor was generated by bubbling a stream of clean, dry air through undiluted test material in a round bottom flask that was heated to 42-48 ° C. Vapor was introduced into a 500 L chamber with an airflow rate of 10 L/min. The chamber was designed such that the rats could be introduced after the chamber had achieved 99% of the maximum vapor concentration. Rats were quarantined for at least 5 days prior to exposure. Body weights were determined prior to exposure and at the end of the 14-day observation period. Rats were individually caged and not fed during the 4-hour exposure period. Rats were observed for health during the exposure and observation period. All rats were killed and submitted to a gross necropsy at the end of the 14-day observation period. No statistical methods were utilized during the test. The nominal concentration was 3.48 mg/L, which was calculated by measuring the weight of test substance vaporized and dividing by the amount of air used during the exposure period. The measured concentration was 0.95 mg/L, which was determined by gas chromatography from a 25 mL solution through which was bubbled 5 L of test air/vapor. Gravimetrically prepared standards in water were used for calibration. It was noted the vapor-air mixture "crystallized" forming a "fine dust" which was 100% respirable. Standard methodology, for the time was utilized. The nominal concentrations and analytical concentrations serve to bracket the actual vapor concentration. It cannot be determined how effective the water was at trapping the test-substance vapor. The "fine dust" was not characterized and probably represents an aerosol. The exposure was probably actually to a vapor-aerosol mixture.
GLP:	No
Test Substance:	1,6-Hexanediamine, purity not reported
Results:	No animals died during the exposure period or the 14-day

observation period. No findings were reported at the necropsy. Rats were reported to gain weight normally during the period with a mean weight gain of 74 grams for males and 24 grams for females.

Based on an experimental vapor pressure of 0.118 mm, saturated vapor would contain 0.75 mg/L at 25°C. At 45 °C, saturated vapor would contain about 5 mg/L test material. As both the measured concentration and nominal concentration were above predicted vapor saturation, and as the investigators reported that the material "crystallized" (its melting point is 42°C so it was possibly in a crystalline form), it was assumed that this was an aerosol/vapor combined exposure. In spite of the investigators stating that the "dust" was 100% respirable there is no evidence that the particle size was in the respirable range.

Combined saturated vapor with aerosol exposure for four hours did not cause any mortality under these conditions.

Reference: Monsanto Corp. (1976). Unpublished Report, Industrial Biotest study No. 8562-081543, "Acute Heated Vapor Inhalation Toxicity Study with Hexamethylene Diamine in Rats" (April 23).

Reliability: Medium because the test atmosphere was not fully characterized.

Additional References for Acute Inhalation Toxicity:

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

National Defense Research Committee (1942). Office of Scientific Research and Development, Progress Report NDCrc-132 (RTECS/MO1180000).

International Labour Office (1983). Encyclopedia of Occupational Health and Safety, Volumes I and II, p. 1752, International Labour Office, Geneva, Switzerland (HSDB/187).

Standard Oil (n.d.). Unpublished data (cited in SIDS Dossier for 1,6-Hexanediamine (http://www1.oecd.org/ehs/sidstable/index.htm accessed on February 19, 2002) and IUCLID (2000). IUCLID Dataset, "Hexamethylenediamine" (February 18)).

Type: **Dermal LD_{50}**

Species/Strain: Rabbits/New Zealand

Exposure Time:	24 hours
Value:	1110 mg/kg (600-2120 mg/kg)
Method:	No specific test guideline was reported; however, a scientifically defensible approach was used to conduct the study. The method used was essentially that of Smyth et al. (1962). Amer. Ind. Hyg. Assoc., 23:95-107 except that 3 rabbits were used per dose and the doses were kept in place by 8-ply gauze patches under a latex rubber film. Fur was removed from the entire trunk of the rabbits by clipping. Rabbits were immobilized during the 24-hour exposure period, after which the patch was removed and the rabbits were caged for the subsequent 14-day observation period. The LD_{50} value and its fiducially range were estimated by the method of Thompson, W. R. (1947). Bacteriol. Rev., 11:115 using the Tables of Weil (Weil, C. S. (1952). Biometrics, 8:249).
GLP:	No Data
Test Substance:	1,6-Hexanediamine, purity not specified
Results:	No additional data.
Reference:	Vernot, E. H. et al. (1977). Toxicol. Appl. Pharmacol., 42(2):417-423.
Reliability:	High because a scientifically defensible or guideline method was used.

Additional References for Acute Dermal Toxicity:

Data from this additional source support the study results summarized above. This study was not chosen for detailed summarization because the data were not substantially additive to the database.

Monsanto Co. (1968). Unpublished report, "Toxicological Investigation of CP 54121", Younger Laboratories, Monsanto Project Number Y-68-20 (February 15).

Data from this additional source were not summarized because the test substance was a mixture or otherwise inappropriate.

DuPont Co. (1974). Unpublished Data, Report No. 720-74, "Acute Skin Absorption Test" (December 17).

Type:	*In Vitro* Skin Irritation/Corrosion
Species/Strain:	Not Applicable
Test System:	Biomembrane
Method:	No official guideline followed; however, followed

instructions of *In Vitro* International, which is sanctioned, by DOT, EPA and FDA.

A pre-qualification assay was conducted to determine that the category of the material for the definitive test was I. The definitive test was conducted by adding the test material to the special vial containing the biomembrane and indicator solution. The test was timed for breakthrough of the membrane indicative of skin corrosion.

Concentration: neat
GLP: No
Test Substance: 1,6-Hexanediamine, purity not specified
Conclusion: Packing Group II, considered corrosive to skin.
Results: The test solution turned color after 30 minutes (30-37 minutes); therefore using the criteria of Category I compounds, this material is placed in "packing group II".
Remark: Study followed standard method, sufficient documentation.
Reference: Monsanto Co. (1966). Unpublished Report, Springborn Laboratories, Study # 3044.599; Monsanto study # SB-96-163, Letter report to Monsanto dated 30 October 1996.
Reliability: High because a scientifically defensible or guideline method was used.

Type: **Dermal Irritation**
Species/Strain: Male and female rabbits/Strain not specified
Method: No specific test guideline was reported; however, a scientifically defensible approach was used to conduct the study.

The test material was applied to the clipped intact skin of six rabbits, three as a powder and three as a 25% aqueous solution. The application site was occluded for 25 hours and the dressing was removed after 24 hours. Observations of skin irritation were conducted by the method of Draize at 1, 24, 48, 72, 120, and 168 hours after removal of the covering.

GLP: No
Test Substance: 1,6-Hexanediamine, purity not specified
Results: The test material was corrosive as powder or as 25% aqueous solution.

All observations of the skin for the three animals exposed to the powder were rated an 8/8 at all the observation times. Animals exposed to the aqueous preparations were scored 2.6/8 (mean of three) at the 1-hour observation and 8/8 at all other observation times. Application of either solid or diluted solution was considered to cause a corrosive effect

on the skin of rabbits after a 24-hour exposure period.

Remark: The exposure time of 24 hours was much longer than the currently recommended exposure time of 4-hours for dermal irritation. As most alkyl amines are considered skin corrosives, the results using this longer exposure time, combined with *in vitro* results, are satisfactory to characterize the skin irritation potential of this material.

Reference: Monsanto Co. (1968). Unpublished Report, "Toxicological Investigation of CP 54121", Younger Laboratories, Monsanto Project Number Y-68-20, (February 15).

Reliability: High because a scientifically defensible or guideline method was used.

Additional References for Dermal Irritation:

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

Standard Oil Co. (n.d.). Data (cited in TSCA Fiche OTS0215309 and OTS0206578).

DuPont Co. (1972). Unpublished Data, Haskell Laboratory Report No. HL-218-72, "Skin Irritation Test on Rabbits" (June 12) (cited in TSCA Fiche OTS0000931).

Industrial Bio-Test Laboratories (1972). IBT Report No. A1854, (July) (cited in TSCA Fiche OTS0206028, OTS0520783, OTS0534489).

Von Oettingen, W. F. (1942). Yale J. Biol. Med., 15:167 (cited in Ceresa, C. and M. de Blasiis. (1948). Med. Lav., 39:162-165).

DuPont Co. (1947). Unpublished Data, Haskell Laboratory Report No. HL-26-47, "Hexamethylene diamine" (April 22) (cited in TSCA Fiche OTS0000931 and OTS0514911).

Goldblatt, M. W. (1949). Unpublished Data (cited in Ceresa, C. and M. de Blasiis (1950). Med. Lav., 41:78-85).

Zeller, H. (1957). Arch. Exp. Pathol. Pharmakol., 232:239-240 (CA52:4930h).

DuPont Co. (1948). Unpublished Data, Haskell Laboratory Report No. HL-8-48, "Acute Toxicity Tests with Hexamethylene diamine" (February 3) (cited in TSCA Fiche OTS0000931).

Vernot, E. H. et al. (1977). Toxicol. Appl. Pharmacol., 42(2):417-423 (HSDB/187).

DuPont Co. (1969). Unpublished Data, Haskell Laboratory Report No. HL-164-69, "Skin Primary Irritation Test" (June 23) (cited in TSCA Fiche OTS0000931).

BASF AG (1959). Abt. Toxikologie, Unpublished Investigation VII/258, 20.02.1959 (cited in IUCLID (2000). IUCLID Dataset, "Hexamethylenediamine" (February 18)).

BASF AG (1955). Abt. Toxikologie, Unpublished Investigation V/113, 25.03.1955 (cited in IUCLID (2000). IUCLID Dataset, "Hexamethylenediamine" (February 18)).

Celanese Chemical Co. (1972). TSCA Fiche OTS0520783 and OTS0534489.

BASF AG (1986). Dept. Toxicology, Unpublished Investigation 85/372 (cited in BASF (1991). AIDA Basic Data Set).

DuPont Co. (1998). Unpublished Data, Haskell Laboratory Report No. HL-1998-01364, "Corrositex *In Vitro* Test" (February 11).

Type:	**Dermal Sensitization**
Species/Strain:	Guinea pig/Strain not specified
Method:	No specific test guideline was reported. Few method details were reported. Initial and final patch tests were performed. A final injection was given after a 10-day rest period.
GLP:	No
Test Substance:	1,6-Hexanediamine, purity not specified
Results:	A 2% aqueous solution caused no irritation or sensitization to guinea pig skin.
Reference:	DuPont Co. (1948). Unpublished Data, Haskell Laboratory Report No. 8-48, "Acute Toxicity Tests" (February 3) (also cited in TSCA Fiche OTS0000931).
Reliability:	Not assignable because limited study information was available.

Type:	**Dermal Sensitization**
Species/Strain:	Human
Method:	Four workers from a nylon factory were examined for dermatitis.
GLP:	No
Test Substance:	1,6-Hexanediamine, purity not specified
Results:	Dermatitis caused by HMDA occurred in four workers in a nylon factory. The condition reappeared rapidly if the same

work was resumed. All 4 subjects had liver disorders and gastric ulcers and/or had undergone surgery for gastric ulcers. Because exposure to the substance was possible and other exposures are not adequately described, no assessment could be made of sensitizing effect.

Reference: Duverneuil, G. and G. Buisson (1952). Arch. Mal. Prof. Med. Trav. Secur. Soc., 13:389-390 (CA47:3571i).

Reliability: Not assignable because limited study information was available.

Additional References for Dermal Sensitization:

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

Zeller, H. (1957). Arch. Exp. Pathol. Pharmakol., 232:239-240 (CA52:4930h).

Engibaryan, L. A. and R. A. Frangulyan (1983). Zh. Eksp. Klin. Med., 23(6):596-599 (CA100:161296z).

Type: **Eye Irritation**

Species/Strain: Male and female rabbits/Strain not specified

Method: No specific test guideline was reported; however, a scientifically defensible approach was used to conduct the study.

The test material (0.1 mL as a 25 aqueous solution) was applied to the right eye of three rabbits (2 males and 1 female). The treated eyes were washed with warm isotonic saline 2, 4, or 30 seconds after application. The eyes were examined using the method of Draize at 1, 24, 48, 72, 120, and 168 hours after treatment.

GLP: No

Test Substance: 1,6-Hexanediamine, purity not specified

Results: The test material was corrosive after 30 seconds as a 25% aqueous solution.

Time of Washing	Irritation Score (110 point basis) At time interval (hours)					
	1	24	48	72	120	168
30 seconds	110	110	110	110	110	110
4 seconds	69	87	87	87	87	87
2 seconds	47	51	47	40	31	19

	The 30-second exposure followed by a saline wash resulted in maximal irritation with no significant recovery. The 2-second exposure resulted in moderate irritation with significant recovery during the limited observation period. The 4-second exposure was intermediate. Based on these data from a 25% aqueous solution, the test material was considered corrosive to the eye.
Reference:	Monsanto Co. (1968). Unpublished Report, "Toxicological Investigation of CP 54121", Younger Laboratories, Monsanto Project Number Y-68-20 (February 15).
Reliability:	High because a scientifically defensible or guideline method was used.

Additional References for Eye Irritation:

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

Standard Oil Co. (n.d.). Data (cited in TSCA Fiche OTS0206578).

Hawley, G. G. (1981). The Condensed Chemical Dictionary, 10th ed., p. 529, Van Nostrand Reinhold Co., New York (HSDB/187).

5.2 Repeated Dose Toxicity

Type:	**13-Week Inhalation Toxicity Study**
Species/Strain:	Rats/Sprague Dawley CD
Sex/Number:	Male and female/15 per sex per concentration level
Exposure Period:	13 weeks
Frequency of Treatment:	6 hours/day, 5 days/week
Exposure Levels:	0, 12, 50, 200 mg/m^3
Method:	No specific test guideline was reported; however, a scientifically defensible approach was used to conduct the study. For the low dose group, an aqueous solution of HMD was placed in a 50-mL glass syringe mounted in a Sage syringe pump and was fed directly into an air atomizing nozzle. Dry air was passed through the atomizer to generate the aerosol. The aerosolized test material was then directed into a 1 m^3 stainless steel and glass Rochester-type chamber and diluted with chamber air. For the two higher dose groups of HMD, a high speed FMI pump was used to deliver the aqueous test material from a glass reservoir to the spray atomizing nozzle.

Dry air, at a flow rate of 15 L/min, was then passed through an atomizer. The resultant aerosol was then directed into the chamber and diluted with the main chamber air. Each chamber had a volume of 760 L. Chamber concentrations of HMD were analyzed at least 3 times/day. Particle size distribution was determined in each chamber 3 times during study week 1 and once weekly thereafter using a cascade impactor.

Rats of each sex were 48 days old on the first day of exposure and were housed individually in stainless steel wire mesh cages. Animals were Sprague-Dawley derived (CD) rats from Charles River (Wilmington, Mass). Food and water were withheld during the 6-hour exposure period, but were available *ad libitum* at all other times. Food, but not water, was withheld overnight prior to blood collection.

Group size was 30 rats (15 of each sex) and four groups were used at target concentrations of 0, 12.5, 50, or 200 mg/m^3. Animals were exposed for 6 hours a day, 5 days/week. The 760 L chambers were operated dynamically at flow rates of 232-290 L/min, which provided one complete air change every 3.4 to 4.3 minutes and a 99% equilibrium time of 15.9 to 19.8 minutes.

Each rat was weighed prior to the study and weekly during the test period. All rats were observed at the end of each exposure period and signs of toxicity were recorded. Rats underwent indirect ophthalmoscopic examination during the pretest period and after 13 weeks of exposure.

Clinical laboratory and hematological determinations were conducted on 5 rats/sex/group pretest and after 5 weeks of HMD treatment. Blood was collected by retroorbital sinus bleeding. The same parameters were measured in all rats surviving until termination. Four hematology parameters and 14 blood chemistry parameters were measured or calculated. Urinalysis examinations were not conducted.

At study termination, all rats underwent a gross necropsy. Organ weights relative to brain and body weights were calculated for 11 organs. Representative samples of approximately 35 tissues were taken. Tissue sections were prepared by conventional histopathologic techniques, stained with hematoxylin and eosin, and examined by light microscopy.

Body weights, hematology values, clinical laboratory parameters, and organ weights were statistically evaluated by a test for analysis of variance and, where appropriate, by the necessary tests for multiple comparison.

GLP: Yes

Test Substance: 1,6-Hexanediamine, purity ≥91%

Results: No specific test guideline was reported; however, a scientifically defensible approach was used to conduct the study.

Mean nominal atmospheric concentrations were 69±13.5, 196±71, and 834±270 mg/m^3 for the 12, 50, and 200 mg/m^3 groups, respectively. The aerodynamic mass median diameter and geometric standard deviation of the aerosol were 1.1 and 3.9, respectively. Greater than 97% of the particles at all exposure levels were considered to be in the respirable range.

Mean measured atmospheric concentrations were 12.8, 51, and 215 mg/m^3 for the 12, 50, and 200 mg/m^3 groups, respectively. The aerodynamic mass median diameters were between 2.61 and 0.11 microns. Greater than 90% of the particles at all exposure levels were considered to be in the respirable range (less than 10 μ). Test substance concentration in the chambers was determined by drawing samples of the test atmosphere through filter paper and titration of the test material with hydrochloric acid to the phenolphthalein endpoint.

Because of exposure-related deaths in another group of rats similarly exposed to 215 mg/m^3, this exposure was terminated during the 7th week of the study. In the high-dose group 13 male and 10 female rats either died or were euthanized moribund between study days 5 and 39. No cause of death was discerned for those rats that died on study. Rats that died exhibited respiratory dysfunction, generalized debilitation, and weight loss. One male rat in the 51 mg/m^3 group was killed *in extremis* on test day 65. All other rats survived until study termination.

No corneal abnormalities attributable to the test substance were observed.

Signs of respiratory and conjunctival irritation were noted in the rats exposed to 51 and 215 mg/m^3. Both the incidence

and severity of the irritation response were increased in rats exposed at 215 mg/m^3. At 215 mg/m^3, rapid, labored, or gasping respiratory patterns were reported.

Significant reduction in body weight gains were observed in male and female rats exposed to 215 mg/m^3 from study week 1 through week 6. A slight (not statistically significant) reduction in body weight gain was observed throughout the study in 51 mg/m^3 female rats and in males in this group through week 8.

After five weeks of exposure, slight hemopoietic stimulation of peripheral blood parameters was observed in rats of each sex exposed to 215 mg/m^3. While the erythrocyte count, hemoglobin, and hematocrit values were elevated above the corresponding control groups, only the female's values were statistically increased. A small increase in mean corpuscular volume and a corresponding decrease in the mean corpuscular hemoglobin concentration were also observed in these groups. The high exposure groups also had slightly, but statistically significant, increases in blood urea nitrogen and serum glutamic pyruvic transaminase activities. Rats exposed to 51 and 12.8 mg/m^3 exhibited no treatment-related hematologic changes at either 5 or 13 weeks. Glucose levels were significantly depressed in the female rats of these two groups when compared to controls only at the 13-week evaluation. The mean values, however, of both treated groups fell within the historical control values for the laboratory and literature reports for this parameter (Wolford, S. T. et al. (1986). J. Toxicol. Environ. Health, 18:161-168).

There were no differences in absolute or relative organ weights considered indicative of an exposure-related response. Treatment-related microscopic lesions were seen only in rats exposed to 215 mg/m^3 and were confined to the trachea, nasal passages, and lungs.

The NOEL was 12.8 mg/m^3 based on reduced body-weight gain and clinical signs of irritation in the 51 mg/m^3 group.

Reference: Johannsen, F. R. et al. (1987). Fund. Appl. Toxicol., 9:504-511.

Monsanto Co. (1979). Report No. BD 79-346 (also cited in TSCA Fiche OTS0001068).

Reliability: High because a scientifically defensible or guideline method was used.

Type:	**13-Week Inhalation Toxicity Study**
Species/Strain:	Rats/Fisher 344 Mice/B6C3F1
Sex/Number:	Male and female/10 rats and 10 mice per sex per concentration level
Exposure Period:	13 weeks
Frequency of Treatment:	6 hours/day, 5 days/week
Exposure Levels:	0, 1.6, 5, 16, 50, or 160 mg/m^3 HDDC (corresponding to 0, 0.5, 1.6, 5, 15, and 51 mg/m^3 hexamethylenediamine)
Method:	No specific test guideline was reported; however, a scientifically defensible approach was used to conduct the study.

HMD was converted to 1,6-hexanediamine dihydrochloride (HDDC) by acidification with concentrated hydrochloric acid under a stream of nitrogen. The final pH was adjusted within the range of 4.5 to 5.5. The 70% aqueous HDDC solution was placed in a 9-L glass reservoir and pressurized with N_2 gas. HDDC was delivered to spray nozzles by a positive displacement metering pump. The nebulizer reservoir was kept in a separate chamber and served as a mixing pleneum where large droplets and non-nebulized liquid were impacted and sedimented out of the test atmosphere before the aerosol was delivered to the inhalation chambers. The HDDC aerosol was mixed with compressed breathing air and supplied at 50 psi to generate an aerosol at a concentration equal to the highest concentration. The resulting aerosol was delivered to the inhalation chambers via PVC tubing. At each chamber, a metered amount of aerosol was removed from the manifold and mixed with the appropriate amount of HEPA/charcoal filtered room air to achieve the desired test concentration.

Concentrations of HDDC in the exposure chamber were monitored by measuring the forward light scatter with RAM-S real-time aerosol monitors and by gravimetric analysis of filter samples from the exposure chambers. Spatial homogeneity of the aerosol within the exposure chambers was measured using calibrated RAM-S monitors. Particle size determinations were obtained for each chamber using an aerodynamic particle sizer.

Groups of 10 male and 10 female rats and 10 male and

10 female mice were exposed 6 hours a day, 5 days a week, for 13 weeks to 1.6, 5, 16, 50, or 160 mg/m^3 of HDDC. Rats and mice were approximately 6 to 7 weeks of age at study start. Food and water were available *ad libitum* during non-exposure periods. During inhalation exposures, rats were housed in stainless steel and glass exposure chambers of 2 m^3 volume with 15 air changes per hour. Chambers were maintained at 72-78ºF and 70-80% relative humidity.

Body weights were recorded at study start, weekly, and at the end of the study. Clinical signs were recorded weekly.

Blood samples were collected from all base study rats at the end of the study. Approximately 10 hematology parameters were measured or calculated and six clinical chemistry parameters were evaluated.

At study termination, a complete necropsy on all treated and control animals were conducted. The thymus, heart, right kidney, lungs, brain, liver, and right testis of each animal were weighed. Organs and tissues were examined for gross lesions and fixed in formalin. Tissues to be examined microscopically were trimmed, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Approximately 40 tissues from the control and high-exposure groups were examined microscopically. The nose/nasal cavity and larynx were examined in lower exposure groups to a no-effect level.

Sperm morphology and vaginal cytology evaluations were performed on base study rats and mice from the control and the 3 highest exposure groups (16, 50, and 160 mg/m^3). Epididymal sperm motility was evaluated at necropsy. The number of motile and non-motile sperm were counted, sperm density was determined, and sperm morphology was examined. Vaginal cytology was evaluated during the week preceding necropsy. Vaginal saline lavage was performed on females for 7 consecutive days prior to scheduled termination. The relative preponderance of leukocytes, nucleated epithelial cells, and large squamous epithelial cells in the lavage fluid were used to identify the stages of the estrous cycle.

Mating trials were performed on rats from the control and from the 3 highest exposure groups (16, 50, and 160 mg/m^3). Mating trial animals were bred for 10 nights (approximately

study days 60-80, weekdays only) prior to the end of the 13-week exposure period. Females were removed from the inhalation chambers and housed overnight in polycarbonate cages with males from the same treatment group (2 females per male). Each morning during the mating period, females were examined for evidence of copulation by vaginal lavage. Females not showing evidence of copulation were mated again each night until they were sperm positive or for a maximum of 10 nights. Following the last day of exposure, females were housed individually in polycarbonate cages until parturition. Male rats and mice were sacrificed at the end of the exposure period without further examination. Females and pups were sacrificed on lactation day 21. Dams and pups were periodically weighed and pups were examined for morphological alterations, viability, and gender. The number of live/dead offspring, percent neonatal survival, mean live pup weight, and sex ratio were recorded.

Organ and body weight data were analyzed using the parametric multiple comparisons procedures of Williams, 1971 and Dunnett, 1955. Clinical chemistry and hematology data were analyzed using the nonparametric multiple comparisons methods of Shirley, 1977 and Dunn, 1964. Jonckheere's test was used to assess the significance of dose-response trends and to determine whether a trend-sensitive test was more appropriate for pairwise comparisons than a test capable of detecting departures from monotonic dose response. The outlier test of Dixon and Massey, 1951 was employed to detect extreme values. Vaginal cytology data were transformed to bring the data into closer conformance with normality assumptions. Treatment effects were investigated by applying a multivariate analysis of variance to the transformed data to test for the simultaneous equality of measurements across dose levels. Continuous, quantitative mating data, such as body weights, were analyzed by Dunnett's t-test for multiple comparisons to a single control group. Discrete, counting mating data, such as litter counts, were analyzed by the Mann-Whitney U nonparametric test. Percentage data, such as fertility and survival indices, were analyzed by the Chi Square test.

Williams, D. A. (1971). Biometrics, 27:103-117.
Dunnett, C. W. (1955). J. Am. Stat. Assoc., 50:1096-1121.
Shirley, E. (1977). Biometrics, 33:386-389.
Dunn, O. J. (1964). Technometrics, 6:241-252.
Dixson, W. J. and F. J. Massey, Jr. (1951). Introduction to

Statistical Analysis, 1st ed., pp. 145-147, McGraw-Hill Book Company, New York.

GLP: Yes

Test Substance: 1,6-Hexanediamine Dihydrochloride, purity 70.9%

Results: Measured concentrations of HDDC in the exposure chambers were within 6% of the target concentrations in all samples. The mass median aerodymanic diameter values for the test concentrations ranged from 1.62 to 1.72 microns.

Rat Data

No mortality occurred during the study. The final mean body weights of most groups of rats were slightly lower than the mean body weights of the controls. These differences, however, were not statistically significant. The only clinical signs of toxicity were rales and nasal discharge that occurred relatively late in the study. Nasal discharge occurred in male rats in the 5 and 16 mg/m^3 groups and in female rats in all exposure groups (including the control), except those in the 160 mg/m^3 group. Similarly, rales occurred in all female groups, but not the exposed males. Because these signs occurred late in the study and because the incidence was not dose related, the signs were not considered to be the result of specific HDDC toxicity.

At necropsy, no compound-related gross lesions were observed. The only consistent organ weight changes were noted in the lungs. However, all control male and female rats had inflammatory lesions to the lungs and had lung weights that were greater than those of historical controls. Sporadic changes in other absolute and relative organ weights were seen but did not appear to be compound related. Histopathological examination revealed changes in the upper respiratory tract (nasal cavity and larynx) in the 50 and 160 mg/m^3 groups. The morphology, incidence, and severity of microscopic lesions were similar for males and females, and there was a dose-related increase in the incidence and severity of these lesions.

Exposure Group (mg/m^3)	0	1.6	5	16	50	160
Male Rats						
Larynx						
Inflammation	1 (2.0)	0	0	0	2 (1.0)	7 (1.4)
Erosion/Ulcer	0	0	0	0	0	2 (2.0)
Hyperplasia	0	0	0	0	0	1 (1.0)
Nasal Passages						
Respiratory Epithelium						
Degeneration	0	0	0	0	3 (1.0)	10 (2.0)
Erosion/Ulcer	0	0	0	0	0	2 (1.0)
Inflammation	2 (1.0)	0	0	2 (1.0)	2 (1.0)	5 (1.4)
Squamous metaplasia	0	0	0	0	0	4 (1.2)
Olfactory Epithelium						
Degeneration	0	0	0	0	1 (1.0)	10 (2.1)
Erosion/Ulcer	0	0	0	0	0	0
Inflammation	0	0	0	0	0	1 (1.0)
Female Rats						
Larynx						
Inflammation	2 (2.0)	0	0	0	0	5 (2.6)
Erosion/Ulcer	0	0	0	0	0	4 (2.0)
Hyperplasia	0	0	0	0	0	1 (3.0)
Nasal Passages						
Respiratory Epithelium						
Degeneration	0	0	0	1 (1.0)	4 (1.2)	8 (1.8)
Erosion/Ulcer	0	0	0	0	1 (1.0)	4 (1.5)
Inflammation	4 (1.5)	0	0	6 (1.7)	8 (1.5)	8 (1.6)
Squamous metaplasia	0	0	0	0	1 (1.0)	4 (1.0)
Olfactory Epithelium						
Degeneration	1 (1.0)	0	0	0	0	9 (2.2)
Erosion/Ulcer	0	0	0	0	0	0
Inflammation	1 (1.0)	0	0	0	0	0

N = 10 for all groups. The number in parentheses is the average severity score with 1 = minimal, 2 = mild, 3 = moderate, and 4 = marked.

At day 4, female rats in the lowest exposure group had a slight decrease in mean platelet count. At day 18, hematocrit values were increased in female rats at the 2 highest exposure groups and segmented neutrophil counts were decreased minimally in male rats in the highest exposure group. By Day 94, there was a significant decrease in leukocyte and lymphocyte counts in females in the highest exposure groups and in segmented neutrophil counts in females in the 3 highest exposure groups (16, 50, and 160 mg/m^3). Female rats in the 2 lowest exposure groups

had increased hematocrit values. A slight decrease in erythrocyte count was noted in male rats in the 16 mg/m^3 group, and a minor increase in mean cell hemoglobin values occurred in female rats in the 160 mg/m^3 group and male rats in the 50 mg/m^3 group.

Clinical chemistry changes on day 4 included a small increase in alanine aminotransferase activity in male rats in the lowest exposure group and a slight increase in the urea nitrogen level in female rats in the 5 mg/m^3 group. By day 18, concentrations of urea nitrogen increased in male rats in the 50 and 160 mg/m^3 groups and female rats in the 5, 16, 50, and 160 mg/m^3 groups. Sorbitol dehydrogenase (SDH) activity was slightly elevated in female rats in the 160 mg/m^3 group. At day 94, alkaline phosphatase activity was slightly increased in male rats in the 1.6, 50, and 160 mg/m^3 groups, and SDH activity was elevated in males in the 50 mg/m^3 group. No other significant clinical chemistry changes occurred in male or female rats at day 94.

Sperm morphology and vaginal cytology examinations did not reveal any compound-related abnormalities.

There was no effect on male or female fertility, body weight of body weight gains, gestation length, litter size, neonatal survival, pup weights, sex ratios of pups, or pup morphology.

Mouse Data

No mortality occurred. The group mean body weights of exposure groups of both sexes were similar in magnitude to those of their respective control groups over the course of the study. No compound-related clinical signs of toxicity were noted.

A statistically significant increase occurred in the absolute and relative lung weights of female mice in the 160 mg/m^3 group. Absolute and relative liver weights were significantly increased in the male mice in the 50 and 160 mg/m^3 groups. Liver weight to body weight ratios were also increased in the male mice in the 5 and 16 mg/m^3 groups. Other changes in organ weights were not considered to be specifically related to HDDC toxicity. No compound-related gross pathological lesions were found. Compound-related microscopic abnormalities were limited to the upper respiratory tract

(larynx and nasal passages) in the 50 and 160 mg/m^3 groups. The morphology, incidence, and severity of these lesions were similar for males and females. There was a dose-related increase in the incidence and severity of these lesions.

Exposure Group (mg/m^3)	0	1.6	5	16	50	160
Male Mice						
Larynx						
Inflammation	5 (1.0)	0	0	2 (1.0)	4 (1.0)	3 (1.0)
Erosion/Ulcer	0	0	0	0	0	4 (1.0)
Hyperplasia	0	0	0	0	0	1 (1.0)
Nasal Passages						
Respiratory Epithelium						
Hyaline Degeneration	0	0	0	1 (1.0)	8 (1.0)	10 (1.8)
Erosion/Ulcer	0	0	0	0	1 (1.0)	6 (1.3)
Inflammation	0	0	0	0	0	3 (1.0)
Olfactory Epithelium						
Hyaline Degeneration	0	0	0	2 (1.0)	8 (1.0)	10 (2.3)
Inflammation	0	0	0	0	0	3 (1.7)
Female Mice						
Larynx						
Inflammation	2 (1.0)	3 (1.0)	5 (1.0)	9 (1.2)	3 (1.0)	2 (2.0)
Erosion/Ulcer	0	0	0	0	0	3 (1.7)
Necrosis	0	0	0	0	0	4 (1.5)
Nasal Passages						
Respiratory Epithelium						
Hyaline Degeneration	0	0	0	0	10 (1.0)	10 (2.0)
Erosion/Ulcer	0	0	0	0	0	4 (1.2)
Inflammation	0	0	0	0	0	2 (1.0)
Olfactory Epithelium						
Hyaline Degeneration	0	0	0	1 (2.0)	10 (1.0)	10 (2.1)
Inflammation	0	0	0	0	0	2 (1.0)

N = 10 for all groups. The number in parentheses is the average severity score with 1 = minimal, 2 = mild, 3 = moderate, and 4 = marked.

No changes in the sperm morphology parameters were observed, with the exception of an increase in sperm motility in the 16 and 160 mg/m^3 exposure groups. However, this change was not dose-related, and the values were within the range of historical controls for NTP studies. Consequently, the increase in sperm motility was not interpreted as an adverse effect.

There was no effect on male or female fertility or male or female body weight or body weight gains. Three female

mice exposed to 16 mg/m^3 and 1 female and 1 male mouse exposed to 50 mg/m^3 died before scheduled sacrifice. However, these deaths were not considered compound related. A statistically significant increase in mean gestation length of mice in the 50 and 160 mg/m^3 groups was noted; however, in the absence of other reproductive toxicity, this effect was not considered biologically significant. There was no effect on litter size, neonatal survival, sex ratio of pups, or pup morphology. Pups in the 160 mg/m^3 exposure group had mean weights similar to that of controls at birth and on lactation day 5; however, mean weights for pups in this group were lower than the controls on lactation days 14 and 21.

Conclusion: The observed NOAEL for respiratory damage was 5 mg/m^3 HDDC (corresponding to 1.6 mg/m^3 HMD).

Reference: NTP (1993). NTP Technical Report on Toxicity Studies: 1,6-Hexanediamine Dihydrochloride, NTP Toxicity Report Series Number 24, NIH Publication 93-3347.

Reliability: High because a scientifically defensible or guideline method was used.

Type: **13-Week Oral Toxicity Study**

Species/Strain: Rats/Charles River albino

Sex/Number: Male and female/15 per sex per concentration level

Exposure Period: 13 weeks

Frequency of Treatment: Daily

Exposure Levels: 0, 50, 150, 500 mg/kg/day

Method: No specific test guideline was reported; however, a scientifically defensible approach was used to conduct the study.

Rat diet containing HMD was prepared twice weekly and fed *ad libitum* for 13 weeks. Abnormal reactions and deaths were recorded daily and clinical signs were recorded weekly. Body weights were recorded on the initial exposure day and weekly thereafter. Food consumption was recorded for 10 rats/sex/group weekly.

Clinical pathology tests were performed on blood samples from 10 rats/sex from high dose and control groups after 42 and 84 days of treatment. Nine hematology parameters and blood chemistry parameters were measured or calculated. Urine samples from 10 males and 10 females from the

control and high dose groups were analyzed at similar time intervals. Urinalysis examination consisted of glucose, albumin, pH, specific gravity, and microscopic elements.

At study termination, all rats underwent a gross necropsy. Absolute and relative organ weights were determined for 9 organs. At necropsy, representative portions of heart, aorta, lungs, trachea, liver, spleen, lymph nodes, pancreas, esophagus, stomach, small and large intestines, kidneys, urinary bladder, pituitary gland, thyroid glands, parathyroid glands, adrenal glands, gonads (testes, ovaries) and associated organs (prostate, seminal vesicles, uterine horns), brain, spinal cord, peripheral nerve, eyes, optic nerves, salivary glands, sternum, bone, skeletal muscle and bone marrow were preserved in 10% neutral buffered formalin. Fixed tissue from each of 10 male and 10 female rats from the control and T-III (500 mg/kg/day) groups were processed, embedded in paraffin, sectioned, and stained with hematoxylin and eosin for microscopic examination.

Body weights, hematology values, clinical laboratory parameters, and organ weights were statistically evaluated by a test for analysis of variance and, where appropriate, by the necessary tests for multiple comparison.

Dose selection: Doses were selected based on a 28-day dosed-feed pilot study at 0, 3, 10, 30, 100 or 300 mg/kg-day using 5 male and 5 female rats per dose group. In this study, no decrease in body weight gain as compared to controls was noted for any treated group.

GLP: No

Test Substance: 1,6-Hexanediamine, purity not reported

Results: No abnormal reactions or treatment-related deaths occurred during the study. No statistically significant differences were noted in food consumption. Although not statistically significant, there was an apparent dose-related decrease in overall weight gain noted in the both the 150 and 500 mg/kg dose groups at the end of the study. During weeks 6 to 11 the 150 mg/kg dose group showed a slightly greater weight gain than control.

No statistically significant differences in hematology or clinical chemistry parameters were measured between high dosage and control rats. Urinalysis parameters were similar between the two groups.

Sporadic, statistically significant differences in absolute or relative organ weights were observed between treated and control groups. Females at 50 mg/kg showed lower absolute gonad weight, higher heart to body-weight ratio at 500 mg/kg, higher kidney to brain weight ratio at 150 mg/kg, higher kidney to body-weight ratio at 150 mg/kg. Males showed higher pituitary gland to body-weight ratio at 150 mg/kg. Since there were neither dose-related patterns nor confirming histopathological findings, it was concluded that none of these differences were treatment-related. No adverse gross or microscopic changes related to treatment were observed up to 500 mg/kg/day.

Remark: The study report is sufficiently detailed to assess the conduct of the study. Information not in the report that would be useful is a description of the actual concentration of test substance added to the feed and the actual doses based on the measured feed consumption. Likewise, neither the stability of the test material in the feed nor the availability of the test substance mixed with feed to the animals was determined. Later studies (multigeneration study), however, demonstrated that the test material was adequately stable in rat diet. The inclusion of reproductive organs in the pathology list is a strength of the study; however, the failure of the study to achieve a LOAEL reduces the usefulness of the pathological investigation relative to determination of specific target organs.

Reference: Johannsen, F. R. and G. J. Levinskas (1987). J. Appl. Toxicol., 7(4):259-263.

Monsanto Co. (1976). Industrial Biotest Report No. BTL-75-106, "28 and 90-Day Feeding Study of Hexamethylene Diamine in Albino Rats" (September 20).

Reliability: High because a scientifically defensible or guideline study was used.

Additional References for Repeated Dose Toxicity:

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

Additional references for repeated dose inhalation studies:

Gage, J. C. (1970). Br. J. Ind. Med., 27(1):1-18 (CA73:12650g).

DuPont Co. (n.d.). Unpublished Data. "Inhalation Toxicity Study."

Tkachenko, A. E. (1976). Gig. Tr. Prof. Zabol., (12):51-52 (CA86:66464m).

Monsanto Co. (1977). Unpublished Data, Industrial Biotest Study Number BTL 75-108, "30-Day Subacute Dust Inhalation Toxicity Study with Hexamethylene Diamine in Albino Rats" (September 19).

Izrailet, L. I. and E. Laivina (1980). Gig. Prof. Zabol., 123-126 (CA94:836t).

Kulakov, A. E. (1965). Gig. Sanit., 30(5):15-20 (CA63:4853b).

Kulakov, A. E. (1967). Biol. Deistvie Gig. Znach Atmos. Zagryaz., (10):15-32 (CA69:12744k).

Osintseva, V. P. et al. (1966). Gig. Sanit., 31(2):89-91; English version, Hyg. Sanit., (2):262-265.

Standard Oil Co. (n.d.). Data (cited in TSCA Fiche OTS0215309 and OTS0206578).

Martynova, A. P. (1957). Gig. Tr. Prof. Zabol., 1(4):23-29 (CA52:1618h).

Hebert, C. D. et al. (1993). Fundam. Appl. Toxicol., 20(3): 348-59 (HSDB/187).

Anon. (1958). Gig. Sanit., 23(11):71.

Verich, G. E. (1979). Gig. Sanit., 11:71-73 (cited in BASF (1991). AIDA Basic Data Set).

Additional references for repeated dose oral studies:

Von Oettingen, W. F. (1942). Yale J. Biol. Med., 15:167 (cited in Ceresa and de Blasiis (1950). Med. Lav., 41:78-85).

DuPont Co. (1948). Unpublished Data, Haskell Laboratory Report No. HL-8-48, "Acute Toxicity Tests with Hexamethylenediamine" (February 3) (cited in TSCA Fiche OTS0000931).

Hejtmancik, M. et al. (1985). Final Report on the Two-Week Dosed Water Repeated Study of 1,6-Hexanediamine in Fisher 344 Rats, dated September 1985.

Hejtmancik, M. et al. (1985). Final Report on the Two-Week Dosed Water Study of 1,6-Hexanediamine in B6C3F1 Mice, dated August 1985.

Ceresa, C. and M. de Blasiis (1950). Med. Lav., 41:78-85 (CA44:8530c).

Ponomareva, T. V. and G. N. Merkushev (1978). Arkh. Anat., Gistol. Embriol., 74(4):47-52 (CA89:72517j).

Shubik, V. M. et al. (1978). Zh. Gig., Epidemiol., Mikrobiol. Immunol., 22(4):374-380 (CA93:20148c).

Shubik, V. M. et al. (1978). J. Hygiene, Epidemiol., Microbio., Immunology, 22:408-414 (cited in SIDS Dossier for 1,6-Hexanediamine (http://www1.oecd.org/ehs/sidstable/index.htm accessed on February 19, 2002).

Additional references for repeated dose dermal studies:

DuPont Co. (n.d.). Unpublished Data. "Repeat Dose Dermal Study."

Tsyrkunov, L. P. (1966). Gig. Tr. Prof. Zabol., 10(10):52-54 (CA66:27422p).

Oppenheimer, G. S. et al. (1955). Cancer Res., 15:333-340.

5.3 Developmental Toxicity

Species/Strain:	Rats/CD Strain from Charles River
Sex/Number:	Female/22 per dose group
Route of Administration:	Oral gavage, as 1.12, 1.84 or 3.0 % w/w solution in water
Exposure Period:	Gestation days 7-16
Frequency of Treatment:	Daily
Exposure Levels:	0, 112, 184, 300 mg/kg/day
Method:	The study protocol and conduct was similar to OECD 414 "Teratology" dated 12 May 1981.

Groups of 22 pregnant rats were orally administered 112, 184, or 300 mg/kg of HMD in a water solution on days 6-15 of gestation. The control group received water only. Rats were approximately 12 weeks at the start of the in-house breeding procedure.

Rats were observed twice daily for signs of toxicity. Body weights were determined on days 7 to 16 and day 22 of gestation. Food consumption was determined at these same intervals during gestation.

Ten-week old rats weighing 176-225 g were quarantined for approximately 2 weeks at no more than two females or 3 males per cage. They were maintained on *ad libitum* food and water and on a light/dark cycle of 14-hour light/10-hour

dark throughout the study. For breeding, a male was housed overnight with one or two females and vaginal smears were taken the morning following each overnight confinement. The morning a female was identified as sperm positive, she was considered as being in Day 1 of gestation and thereafter housed individually. A sufficient number of sperm positive females was obtained by breeding for 5 consecutive days. The rats that were sperm positive on a given day were randomly assigned to a treatment group on the day that treatment was to begin.

The maternal parameters assessed during the study included body weight, feed consumption, clinical signs, corpora lutea, implantations, and resorptions.

The fetal parameters assessed during the study included litter size, placental weight, gross malformations, fetal crown-rump length, fetal body weight, sex, visceral examinations, and skeletal examination.

The incidence of specific maternal observations was analyzed by the Fisher Exact Probability Test or the Chi-square Test as appropriate. For this analysis the dam was counted in the observation category if she evidenced the specified toxic sign or abnormality any time during the treatment or post-treatment periods. A single factor analysis of variance was performed on maternal body weight, maternal body weight change at different points in gestation, maternal food consumption at different intervals, corpora lutea counts/litter, percent dead or resorbed fetuses/litter, fetal body weight, fetal crown-rump length, and on the percentage of occurrences within litters of specific fetal observations. All data that were in the form of a percentage of occurrence within a litter were transformed by the inverse sine transformation prior to application of analysis of variance. Where the analysis of variance yielded a significant F ratio, treated group means, based on transformed data where appropriate, were individually compared to that of the control group by Dunnett's t test.

A dose-range-finding study was conducted using groups of 4-6 mated CD rats dosed at 0, 112, 225, 450 or 900 mg/kg per day from day 7-16 of pregnancy and were killed on day 21. The uterus was opened and the live fetuses removed, weighed and examined externally, and their crown-rump length and sex were determined. Dosages of 450 or

900 mg/kg/day were lethal to all dams, no maternal deaths occurred at lower doses. There was a slight, but statistically insignificant reduction in body weight gain at 225 mg/kg/day on days 8, 9, and 10. Food consumption was unaffected except at the lethal doses. None of the fetal parameters was significantly affected in surviving dams.

GLP: Yes

Test Substance: 1,6-Hexanediamine, purity not specified. Received as an 85.5 % w/w aqueous solution.

Results: Maternal Findings:

One control, one mid-dose, and two high-dose dams died during the study. The control and mid-dose deaths were thought to result from gavage error based on timing of death and lack of clinical signs previously. Body weight gain and food consumption was significantly decreased in high-dose animals from day 10 to the end of the study. Mid-dose dams consistently showed a reduction of body weight gain as compared to controls but this was not statistically significant. Feed consumption was comparable in all groups except there was a statistically significant reduction in feed consumption for high-dose dams at the day 7-10 and the day 10-13 intervals; and for the mid-dose dams at the day 10-13 interval. Other clinical observations indicative of toxicity occurred commonly only in the high-dose dams and consisted of hunching, unkempt fur, red stained fur, wheezing and respiratory rattle.

Fetal Findings:

Litter size was comparable in all groups. In the high-dose group, fetal body weights were decreased. Sex ratio, crown-rump length, and percent dead or resorbed fetuses were unaffected by treatment. Preimplantation loss was significantly lower in the high-dose group, but high in the control group.

A summary of some of the reproductive outcomes (means/litter) are provided in the tables below:

Dosage (mg/kg)	0	112	184	300
Corpora lutea:	16	15	15	15
Implantations:	14	15	15	15
Total No. of Fetuses:	NR	NR	NR	NR

Postimplantation Loss (% Dead or Resorbed)	3.8	7.6	5.1	2.4
Total No. of Live Fetuses:	14	14	14	14
Mean Fetal Weight (g):	5.62 (m) 5.34 (f)	5.39 (m) 5.09 (f)	5.35 (m) 5.15 (f)	5.18 (m) 4.96 (f)
Sex Ratio (No. of Males/Total No.):	.50	.52	.51	.50
Fetal crown-rump length (mm)	42 (m) 41 (f)	42 (m) 41 (f)	42 (m) 41 (f)	42 (m) 41 (f)
m = male and f = female NR = Not Reported				

External effects consisted of a single case of microcaudia in the high dose group; almost entire tail missing. Focal discoloration was observed in 8/21, 4/22, 3/21, and 2/20 litters for control to high-dose groups respectively.

Visceral findings are detailed in the table below:

Finding	Dosage Group (mg/kg)			
	0	112	185	300
Atypical shape trachea	0/21	0/22	1/21	1/20
Enlarged esophagus	0/21	0/22	1/21	1/20
Atypical position of esophagus	0/21	0/22	1/21	0/20
Major vessel abnormal	0/21	0/22	0/21	1/20
Trabeculation at or near conus	7/21	9/22	8/21	8/20
Heart compressed	2/21	4/22	5/21	5/20
Substance in pericardial space	2/21	6/22	6/21	6/20
Lungs not inflated	1/21	1/22	4/21	4/20
Herniated diaphragm	0/21	1/22	0/21	0/20
Blood in stomach or peritoneal cavity	0/21	0/22	0/21	2/20
Liver spotty	3/21	4/22	7/21	11/20*

Kidney large and/or underdeveloped	2/21	5/22	1/21	2/20
Bladder distended	2/21	6/22	14/21*	8/20
Atypical shape trachea	1/21	5/22	0/21	2/20
Ureters distended	4/21	3/22	1/21	1/20
Testicles asymmetric or atypical position	0/21	0/22	1/21	1/20
* = Statistically significant				

There were no major skeletal effects noted other than the single high-does case of microcaudia noted in external observations. Skeletal findings are detailed in the table below:

Finding	Dosage Group (mg/kg)			
	0	112	185	300
Slight or non-ossification of skull bone	2/21	3/22	6/21	2/20
Weakly ossified maxillary or mandibular process	1/21	0/22	1/21	1/20
Weakly or non-ossified ear ossicles	14/21	20/22	17/21	17/20
Weakly or non-ossified forelimb phalanges	16/21	17/22	18/21	15/20
Weakly or non-ossified hindlimb phalanges	19/21	22/22	21/21	19/20
Weakly or non-ossified metatarsals	12/21	18/22	15/21	13/20
Weakly or non-ossified or split or small hyoid	14/21	20/22	17/21	17/20
14 Rib present	7/21	15/22	13/21	8/20
Non-ossified, fused or abnormal shape ribs	0/21	0/22	1/21	1/20

Asymmetrical, unarticulated small or weakly ossified sternebra	19/21	18/22	20/21	19/20
Weakly or non-ossified or fused lateral components of vertebral column	0/21	0/22	1/21	1/20
Weakly or non-ossified or unarticulated or bilobed cervical vertebral centra	20/21	22/22	21/21	20/20
Only affected component of above was weakly-ossified category	8/21	14/22	17/21*	17/20*
Weakly or non-ossified or unarticulated or bilobed thoracic and lumbar vertebral centra	14/21	20/22	17/21	17/20
Unarticulated centrum-lateral component of sacral and caudal vertebral	14/21	20/22	17/21	17/20
* = Statistically significant				

Summary of fetal data for major external, visceral, and skeletal abnormalities.

Parameter	Dosage Group (mg/kg)			
	0	112	185	300
External Abnormalities	0/271	0/301	0/293	1/289
Visceral Abnormalities	0/134	1/150	2/146	1/144
Skeletal Abnormalities	0/137	3/151	1/147	2/145

Most of the fetal observations in this study can be subsumed under the headings of anatomical variations or delays in ossifications. In a few cases the nature of the observation was such that it would typically be classified as an abnormality as opposed to a variant or a delay. For the external examinations only microcaudia would be so classified. The visceral abnormalities were diaphragm hernia, an abnormality in the

course of the subclavian artery, and possibly the atypical position and enlargement of the esophagus. Skeletal abnormalities included one case of an abnormal fusion of 2 adjacent ribs and vertebrae associated with the absence of a vertebra and the corresponding ribs. In a second case 1 rib was abnormally shaped. The table above summarizes the abnormalities by dosage level for each type of examination, the number of fetuses that were observed to have any of the specified type of abnormalities. Whether analyzed in terms of percent affected fetuses/litter, total number affected fetuses/group, or number of affected litters/group, there were neither significant differences between the control group and the individual test groups nor between the controls and the combined test groups in the incidence of these abnormalities.

Treatment with HMD at a dosage of 300 mg/kg/day on days 7-16 of gestation induced maternal toxicity as evidenced by reduced body weight gains, transiently decreased food consumption, clinical observations, and by the death of approximately 10% of the animals treated at this dosage level.

Dosage below 300 mg/kg/day had no statistically significant effects on the dams; however, the initial dosing at the mid dose level caused a transient mean body-weight loss of 2 grams on day eight of gestation.

Fetuses of dams treated with 300 mg/kg/day were slightly retarded in development as evidenced by body weight, limited retardation of skeletal development, and possibly by liver spottiness.

A dosage of 112 mg/kg/day clearly had no effect on the fetuses and only the delay in ossification of cervical vertebral centra precluded the categorization of 184 mg/kg/day as a NOEL.

For the CD rat, which is susceptible to teratogens as was confirmed by a concurrently evaluated positive control group for which a separate report was prepared, HMD was not a specific developmental toxin when administered on days 7-16 of gestation via the oral route.

The NOAEL for maternal toxicity was 112 mg/kg/day. The LOEL was 184 mg/kg/day, as evidenced by marginally reduced body weight gain and feed consumption at 184 mg/kg.

	The NOAEL for fetal toxicity was 112 mg/kg/day. The LOEL was 184 mg/kg/day based on slightly retarded ossification.
Reference:	Johannsen, F. R. and G. J. Levinskas (1987). J. Appl. Toxicol., 7(4):259-263. Monsanto Co. (1979). IITRI Project No. L8041, Report L8042, Life Sciences Research Institute. "A Teratology Study in Rats" (August).
Reliability:	High because a scientifically defensible or guideline method was used.

Additional References for Developmental Toxicity:

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

David, R. M. and H. d'A. Heck (1983). Toxicol. Lett., 17(1-2):49-55 (CA99:135030z)

Johannsen, F. R. and G. J. Levinskas (1987). J. Appl. Toxicol., 7(4):259-263.

Monsanto Chemical Co. (n.d.). Data (cited in AIHA (1999). American Industrial Hygiene Association, The AIHA Emergency Response Planning Guidelines and Workplace Environmental Exposure Level Guides Handbook, AIHA, Fairfax, VA).

5.4 Reproductive Toxicity

Species/Strain:	Rats/Charles River COBS CD, Portage Michigan
Sex/Number:	Males and females/26 per sex per group
Route of Administration:	Oral Feeding
Exposure Period:	F_0 – 56 days prior to mating Total of 40 weeks
Frequency of Treatment:	Continuously in feed
Exposure Levels:	0, 50, 150, 500 mg/kg/day
Method:	No specific test guideline was reported; however, a scientifically defensible approach was used to conduct the study. A 78% solution of HMD in water was used to prepare the test diets. The test substance was weighed, diluted with ethanol, and mixed with ground rodent chow in a Hobart mixer to form a premix. This premix was further diluted with additional feed to obtain the required dietary

concentrations. Test diets were prepared weekly for the control, 50, and 150 mg/kg groups. The diet for the 500 mg/kg group was prepared every 4 days in order to maintain adequate levels of the test material in the diet. Diets were analyzed for homogeneity, stability, and concentration of the test material. Stability analysis showed that the lower concentrations (0.640 and 2.74 g/kg feed) had 10-day stabilities of 95 to 103%; however, the higher concentration (16 g/kg feed) only showed a 10-day stability of 72%. The higher concentration was adequately stable for 4 days (<14% loss).

The control group received the basal laboratory diet with an ethanol (solvent) concentration equivalent to that in the high dose diet.

The F_0 generation contained 26 males and 26 females in each group. The rats were housed in environmentally controlled rooms with 12-hour photoperiods and given free access to food and water. The F_0 rats were approximately 8 weeks old at the start of treatment. Body weights and food consumption were recorded at regularly scheduled intervals, usually weekly.

After a minimum of 56 days of treatment, the F_0 rats were mated to produce the F_1 offspring. Each F_0 male was cohabited with a female from the same treatment group for up to 20 days. Females were examined for evidence of copulation as monitored by vaginal smears or copulatory plugs. Day 0 of gestation was defined as the day evidence of copulation was confirmed. At this point, the female was placed in a plastic cage containing wood chips as nesting material. After the mating period, males were individually housed and continued on treatment until the completion of parturition, when fertility was evaluated.

Pregnant F_0 females were allowed to give birth to F_1 pups. The day all pups were delivered was designated as day 0 of lactation. Litters were examined for size, still births, and gross anomalies. Litter size was reduced to a total of 8 pups of equal sex, when possible, on lactation day 4. Pups were housed with their mothers and weighed at intervals for 3 weeks after birth. Afterward, 26 pups of each sex from each group were selected to become the F_1 parents of the F_2 generation.

After a minimum of 98 days of treatment the F_1 parents were mated to produce the F_2 offspring, as described above. The F_2 pups were sacrificed on lactation day 21.

Gross necropsies were performed on F_0 and F_1 parents as well as F_2 pups. The following tissues were taken from F_0 and F_1 rats for histopathological evaluation: kidneys, liver, lung, ovaries, prostate, seminal vesicles, spleen, testes with epididymis, uterus, and vagina.

Body weight and litter size were statistically evaluated with analysis of variance and Dunnett's tests. Fertility indices were evaluated with χ^2 test, with Yates' correction, or Fisher's exact probability test. Pup survival was evaluated with the Mann-Whitney U test.

GLP: Yes

Test Substance: 1,6-Hexanediamine, 78.02% solution in water

Results: Dietary analysis indicated that greater than 90% of the target concentration of hexamethylenediamine were fed to rats in all groups. The actual doses consumed, however, averaged between 123 and 132% of the target doses in these groups.

No treatment-related mortality was observed in any of the groups. Some deaths occurred, however, they were singular events in specific groups and there was no pattern indicative of a dose-response relationship. Mortality ratios for the F_0 males were 0/26, 1/26, 1/26, and 0/26 for the 0, 50, 150, and 500 mg/kg groups, respectively. Mortality ratios for the F_0 females were 0/26, 0/26, 0/26, and 0/26 for the 0, 50, 150, and 500 mg/kg groups, respectively. Mortality ratios for the F_1 males were 0/26, 0/26, 0/26, and 0/26 for the 0, 50, 150, and 500 mg/kg groups, respectively. Mortality ratios for the F_1 females were 1/26, 1/26, 0/26, and 0/26 for the 0, 50, 150, and 500 mg/kg groups, respectively.

Body weights of male F_0 and F_1 rats in the 500 mg/kg group were reduced by about 10%, relative to control values, at the end of study weeks 15 and 38. The body weights of females, in contrast, were comparable to control values at these intervals. During gestation, the females weight gain was reduced by about 10% in the high-dose group.

Fertility was not adversely affected by the dietary administration of hexamethylenediamine over 2 generations. The F_0 and the F_1 litter size in the 500 mg/kg

group was significantly reduced without an increase in the number of dead pups. There was no biological meaningful or statistically significant differences in the number of viable and dead pups on lactation day 1, as compared to control for either generation in the mid and low-dose treatment groups. Pup survival was not significantly reduced in any of the treated groups. At birth, pup body weights were not adversely affected by treatment, but during lactation, reduced weights were apparent in pups of each sex from the high dose group.

No meaningful differences were noted between the control and treated rats of either generation with regard to antemortem observations, copulatory interval, gestation length, nesting and nursing behavior, and appearance of the pups. No treatment related effects were noted on testes weights and no effects were noted by macroscopic or microscopic examination of tissues evaluated.

Summaries of reproductive outcomes for the F_0 and F_1 generations are provided in the tables below:

F_0 Generation

Concentration (mg/kg):	0	50	150	500
Copulation Index (%):	100	100	100	96
Fertility Index Female (%):	88	92	88	92
Fertility Index Male (%):	88	92	88	92
Gestation Length (days):	22	22	22	22.1
Implantation sites:	NR	NR	NR	NR
Pregnancy Rate (%):	88	92	88	92
Mean Litter Size:	14.0	15.2	15.6	12.0
Gestation Index (%):	NR	NR	NR	NR
Mean % Born Alive:	99	99	97	98
0-4 Day Viability (%):	99	98	99	99
Weaning Viability Index (%):	100	100	99	100
Sex Ratio (% males):	NR	NR	NR	NR
NR = Not Reported				

F_1 Generation

Concentration (mg/kg):	0	50	150	500
Copulation Index (%):	84	84	92	100
Fertility Index (%):	77	69	73	81
Gestation Length (days):	22.1	22.3	22.1	22.2
Implantation sites:	NR	NR	NR	NR
Pregnancy Rate (%):	77	69	73	81
Gestation Index (%):	NR	NR	NR	NR
Mean % Born Alive:	98	99	98	100
0-4 Day Viability (%):	99	99	99	99
Weaning Viability Index (%):	100	100	100	99
Sex Ratio (% males):	NR	NR	NR	NR
Litter size – Day 0 (pups/litter)	13.8	13.1	13.2	11.7
Litter size – Day 4 (pups/litter)	13.7/ 8.0*	12.9/ 7.9	13.1/ 7.8	11.6/ 8.0
Litter size – Day 21 (pups/litter)	7.9	7.9	7.7	7.9
Pup Weight – Day 0 (g/pup)	6.4	6.4	6.3	6.5
Pup Weight – Day 4 (g/pup)	10.1/ 10.1*	10.8/ 10.7	10.4/ 10.4	10.3/ 10.3
Pup Weight – Day 21 (g/pup)	53.0/ 50.5**	54.5/ 52.1	55.0/ 53.1	49.6/ 47.6

* = Litter parameter before reduction/litter parameter after reduction.
** = Male weight/female weight
NR = Not reported

F_2 generation

Concentration (mg/kg):	0	50	150	500
Litter size – Day 0 (pups/litter)	13.0	13.5	13.1	11.0
Litter size – Day 4 (pups/litter)	12.9/ 8.0*	13.4/ 7.6	12.9/ 7.6	10.9/ 7.8
Litter size – Day 21 (pups/litter)	7.9	7.6	7.6	7.7
Pup Weight – Day 0 (g/pup)	6.3	6.3	6.1	6.3
Pup Weight – Day 4 (g/pup)	9.8/ 9.7*	10.1/ 10.3	9.9/ 9.9	10.3/ 10.3
Pup Weight – Day 21 (g/pup)	53.6/ 51.5	55.3/ 54.0	54.2/ 50.4	51.5/ 49.0

* = Litter parameter before reduction/litter parameter after reduction.
** = Male weight/female weight

	The NOEL was 150 mg/kg/day.
Reference:	Short, R. D. (1991). Fundam. Appl. Toxicol., 16(3):490-494 (DART/9831).
	Monsanto Co. (1985). International Research and Development Corp. Report IR-83-146, "Hexamethylene Diamine, Two Generation Rat Reproduction Study" (September 20).
Reliability:	High because a scientifically defensible or guideline method was used.

Additional Reference for Reproductive Toxicity:

Data from this additional source support the study results summarized above. This study was not chosen for detailed summarization because the data were not substantially additive to the database.

NTP (1993). NTP Technical Report on Toxicity Studies: 1,6-Hexanediamine Dihydrochloride, NTP Toxicity Report Series Number 24, NIH Publication 93-3347.

5.5 Genetic Toxicity

Type:	***In vitro* Bacterial Reverse Mutation Assay**
Tester Strain:	*Salmonella typhimurium* TA100, TA1535, TA1537, TA98
Exogenous Metabolic Activation:	With and without Aroclor-induced rat and hamster liver S9
Exposure Concentrations:	0, 33, 100, 333, 1000, 3333, 6666, 10,000 µg/plate
Method:	No specific test guideline was reported; however, a scientifically defensible approach was used to conduct the study.
	The test compound was tested in a preincubation assay (study 1). The incubation mixture containing S9 mix or buffer, bacterial culture, and the solvent or the chemical, was mixed and allowed to incubate without shaking at 37ºC for 20 minutes, at which time top agar was added. The contents of the tubes were mixed and poured onto minimal glucose bottom agar in petri dishes and the dishes were incubated at 37ºC for 48 hours. Concurrent solvent (distilled water for study 1 and DMSO for study 2) and positive controls (sodium azide, 4-nitro-o-phenylenediamine, 9-aminoacridine, 2-aminoanthracene) were tested with and

	without the metabolic activation systems. Potassium chloride was a coded negative control. Three plates were tested per dose level. All assays were repeated no less than 1 week after completion of the initial test (study 2). The chemical was initially tested with strain TA100 in the presence or absence of the metabolic systems, over a wide range of doses with an upper limit of 10,000 µg/plate. The S9 mix contained S9 fraction, $MgCl_2$, KCl, NADP, glucose-6-phosphate, NaH_2PO_4, and distilled water. The criteria for data evaluation was 1) mutagenic response: a dose-related, reproducible increase in the number of revertants over background, even if the increase was less than 2-fold or 2) nonmutagenic response: when no increase in the number of revertants was elicited by the chemical.
GLP:	Unknown
Test Substance:	1,6-Hexanediamine, purity 98+%
Results:	Negative
Remarks:	HMDA is nonmutagenic when tested in the presence and absence of metabolic activation. Slight to total clearing of the background bacterial lawn occurred in most cultures at the highest dose (10,000 µg/plate) during the preliminary dose setting experiment. The chemical was toxic at doses of 3333 µg/plate and greater in both studies.
Reference:	Mortelmans, K. et al. (1986). Environ. Mutagen., 8(Suppl. 7):1-119. NTP (1993). Toxicity Report Series 24, NIH Publication 93-3347, "Technical Report on 1,6-Hexanediamine Dihydrochloride."
Reliability:	High because a scientifically defensible or guideline method was used.
Type:	***In vitro* Sister Chromosome Exchange and Chromosome Aberration Assay**
Cell Type:	Chinese hamster ovary cells
Exogenous Metabolic Activation:	With and without Aroclor-induced rat liver S9
Exposure Concentrations:	Induction of sister chromatid exchanges (SCEs): 0, 16, 50, 160, 500 µg/mL (Trial 1, -S9) 0, 5, 160, 500 µg/mL (Trial 1, +S9) 0, 50, 160, 500, 1000 µg/mL (Trial 2, +S9)

Induction of chromosome aberrations:
0, 160, 300, 500 µg/mL (all trials)

Method: No specific test guideline was reported; however, a scientifically defensible approach was used to conduct the study. The testing was performed as reported by Galloway et al. (1987). Environ. Mol. Mutagen., 10(Suppl. 10):1-175.

Chinese hamster ovary cells (CHO) were incubated with HMD for analyses of sister chromatid exchanges (SCEs) and chromosomal aberrations (Abs), both in the presence and absence of Aroclor 1254-induced rat liver S9 mix.

Mitomycin C and cyclophosphamide were used as positive controls.

In tests without metabolic activation, the test chemical was left in the culture medium until colcemid addition, whereas in tests with activation the test chemical was added along with S9 mix for only 2 hours at the beginning of the test.

SCE Test: 5-Bromodeoxyuridine (BrdUrd) was added 2 hours after addition of the test chemical (without S9) or immediately after the S9 mix plus chemical had been removed. The chemical treatment periods were approximately 25 hours without S9 and 2 hours with S9. The total incubation time with BrdUrd was 25-26 hours, with colcemid present during the final 2-4 hours. Immediately before the cells were harvested, the cell monolayers were examined, and the degree of confluence and availability of mitotic cells were noted. Cells were collected by mitotic shake-off. After a short treatment with hypotonic solution, cells were fixed in 3:1 methanol:glacial acetic acid. Slides were stained in Hoechst 33258 and exposure to black light, and then stained with Giemsa. All slides were coded before being scored.

Aberration Test: Cells were collected by mitotic shake-off, stained with Giemsa, and coded.

Statistical analyses were conducted on the slopes of the dose-response curves. An SCE frequency 20% above the concurrent solvent control value was chosen as a statistically conservative positive response. If an increase of 20% or greater occurred at a single dose, the response was considered weak evidence of genotoxic activity. If increases

	occurred at 2 or more doses, the trial was determined to be positive. Chromosome aberration data were presented as percentage of cells with aberrations. Statistical analyses were conducted on both the dose-response curve and individual dose points. For a single trial, a statistically significant difference for 1 dose point and a significant trend were considered weak evidence for a positive response. Significant differences in 2 or more doses would indicate that the trial was positive.
GLP:	Yes
Test Substance:	HDDC (1, 6-Hexanediamine dihydrochloride), purity 70%
Results:	Negative
Remarks:	No significant increases in SCEs or aberrations were observed, with or without S9. In the chromosome aberration test with S9, both trials showed an increase in total aberrations at the highest concentration tested (500 µg/mL). In both of these trials, however, these aberrations occurred in fewer than 5% of the total cells scored. Hence, the percentage of cells with aberrations (the endpoint evaluated) was not sufficiently elevated to be considered as a positive response.
Reference:	NTP (1993). NTP Technical Report on 1,6-Hexanediamine Dihydrochloride, Toxicity Report Series 24, NIH Publication 93-3347.
Reliability:	High because a scientifically defensible or guideline method was used.
Type:	**CHO/HGPRT Forward Cell Gene Mutation Assay**
Cell Type:	Chinese Hamster Ovary, clone K1
Exposure Period:	Five hours
Doses:	Rangefinder: 0, 3, 9, 30, 91, 304, 912, 3039 and 9116 µg/mL Definitive 1: 0, 50, 100, 200 or 250 g/mL (without activation) and 0, 100, 300 or 600 g/mL (with activation) Definitive 2: 0, 25, 50, 100, 175 and 250 g/mL (without activation) and 0, 50, 100, 300, 450 and 600 g/mL (with activation)
Exogenous Metabolic Activation:	0, 1, 2, 5, and 10% metabolic activation (liver S9 at > 30 mg protein/mL) were tested in rangefinder and definitive test 1, 5% level used in definitive test 2, homogenates were prepared from Aroclor 1254 induced rat livers.
Method:	No specific test guideline was reported; however, a scientifically defensible approach was used to conduct the study. Cells for testing were obtained from cultures having a stable low spontaneous gene-mutation frequency. Initial

	rangefinding studies at 8 dose levels in the absence and presence of various quantities of metabolic activating S-9 fraction were conducted using an incubation time of 5 hours in the presence of test substance. Cytotoxicity was evaluated by a reduction in the colony-forming ability of the cells after plating. After the initial cytotoxicity evaluation, duplicate cultures of cells were incubated with HMD, in the absence of metabolic activation, at concentrations of 0, 50, 100, 200 or 250 μg/mL. Duplicate cultures of cells were incubated with test substance in the presence of metabolic activation at concentrations of 0, 100, 300 or 600 μg/mL. Four metabolic activation S-9 concentrations, over a ten-fold range were used at each test substance concentration. After washing, a 19-hour incubation in fresh media, and plating followed by 7-8 days of incubation on 6-TG containing plates, colonies were fixed with methanol, stained with crystal violet and counted. Mutation frequencies, cytotoxicity and plating efficiency were evaluated and doses selected for a confirmatory assay. In the confirmatory assay triplicate cultures at TS concentrations of 0, 25, 50, 100, 175 and 250 μg/mL were evaluated in the absence of metabolic activation and concentrations of 0, 50, 100, 300, 450 and 600 μg/mL were evaluated in the presence of 1 level of metabolic activation. Expression of mutation, plating and processing were as in the initial assay. Positive controls were DMN at 100 μg/mL in the absence of metabolic activation and EMS at 200 μg/mL in the presence of metabolic activation.
GLP:	Yes
Test Substance:	Hexamethylenediamine, purity not specified
Results:	Negative
Remarks:	No mutagenic activity in this assay. No increase was found in the mutant frequency expressed as mutant per number of clonable cells or as mean mutation frequency. The controls gave results as expected.
Reference:	High because a scientifically defensible or guideline method was used.
Reliability:	Pharmakon Research International, Inc. (1984). "CHO/HGPRT Mammalian Cell Forward Mutation Assay PK-84-227 Hexamethylene diamine," Sponsored by Monsanto Co, (June 25).

Additional References for *In vitro* Genetic Toxicity:

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

Monsanto Corp. (1976). Unpublished Report, Medical Project No: LF76 206, "Mutagenicity Plate Assay: Hexamethylene diamine."

DuPont Co. (1975). Unpublished Data, Haskell Laboratory Report No. 378-75, "*In Vitro* Microbrial Mutagenicity Studies" (July 10).

DuPont Co. (1992). Unpublished Data, Haskell Laboratory Report No. 103-92, "Mutagenicity Testing in an Abbreviated (1 Trial) *Salmonella typhimurium* Plate Incorporation Assay" (February 12).

BASF AG (1981). Unpublished Report 81/229, Project No. 21001 (December) (cited in IUCLID (2000). IUCLID Dataset "Hexamethylenediamine" (February 18) and cited in SIDS Dossier for 1,6-Hexanediamine (http://www1.oecd.org/ehs/sidstable/index.htm accessed on February 19, 2002)).

Murphey-Corb, M. et al. (1983). Environ. Mutagen., 5(1):101-109 (CA98:193096r).

BASF AG (1980). Abt. Toxikologie, Unpublished Investigation 79/520, 03.04.1980 (cited in IUCLID (2000). IUCLID Dataset, "Hexamethylenediamine" (February 18)).

BASF AG (1980). Abt. Toxikologie, Unpublished Investigation 79/519, 11.07.1980 (cited in IUCLID (2000). IUCLID Dataset, "Hexamethylenediamine" (February 18)).

BASF AG (1980). Unpublished Report (cited in SIDS Dossier for 1,6-Hexanediamine (http://www1.oecd.org/ehs/sidstable/index.htm accessed on February 19, 2002)).

Type:	***In vivo* Bone Marrow Chromosome Study in Rats**
Species/Strain:	Rats/Sprague-Dawley CD (Charles River, Kingston)
Sex/Number:	Male and female/24 per sex per dose level
Route of Administration:	Gavage
Concentrations:	0, 75, 250, or 750 mg/kg
Method:	No specific test guideline was reported; however, a scientifically defensible approach was used to conduct the study. The rats were approximately 62 days old at initiation of the study. Rats were randomized into test groups consisting of

24 males and 24 females per dose level and control. The positive control group (cyclophosphamide, 40 mg/kg) consisted of 6 males and 6 females. The test material was administered by gavage as a solution in water. The test material was 85.33% pure. A correction factor based on the percent active ingredient was used for preparation of the dosing solutions. Dose levels were 0, 75, 250, or 750 mg/kg body weight. Six rats of each sex the control and test groups were sacrificed by carbon dioxide asphyxiation at 6, 12, 24, and 48 hours after dosing. Two hours prior to sacrifice animals received an i.p. injection of colchicine (2 mg/kg bw). Positive controls were sacrificed only at the 24-hour post-treatment interval.

Immediately following sacrifice, bone marrow cells were collected from femurs of each animal. Cells were processed, fixed with 3:1 methanol:glacial acetic acid, and stained with Giemsa. Cells were read blind and the target was to, whenever possible, examine at least 60 metaphase cells from each of 5 animals in each group. The 48-hour sacrifice cells were not scored as there was no evidence of cell-cycle delay.

Upon completion of all scoring, the slides were decoded and the data were analyzed statistically. The mean mitotic indices, mean modal numbers, percent aberrant cells, and the mean number of aberrations per cell for each group were statistically compared using the Kruskal-Wallis nonparametric analysis of variance and nonparametric pairwise group comparisons (KW-ANOVA). Body weight data were analyzed by analysis of covariance (ANCOVA). All tests were one-tailed at the 95% confidence interval ($p < .05$).

GLP: Yes

Test Substance: Hexamethylenediamine, purity 85.33%

Results: Negative

Remarks: The acute oral administration of 75, 250 and 750 mg/kg body weight of hexamethylenediamine to male and fema1e rats induced no significant increases in the frequency of chromosomal aberrations. Some toxic effects were noted in the clinical observations and the loss of body weight of the treated animals. One rat from the 250 ppm group and one rat from the 750 ppm group died while on study. No significant differences were observed between the vehicle control and test groups when comparing modal numbers or mitotic index. Therefore, under the conditions of this study. hexamethy1ene diamine was not clastogenic at any of the

levels tested.

Rats initially weighed about 275 g (males) or 215 g (females).

The following mean bodyweight changes were recorded 24 hours after dosing:

Dose (mg/kg)	Body Weight Change (g): Males	Body Weight Change (g): Females
0	+1.8	+0.7
75	+1.5	-4.7
250	-2.7	-15.7*
750	-30.7*	-22.3*

* = statistically significant $p < 0.01$

Summary data for the results of the 24-hour sacrifice are given in the following table.

Dose	Aberrant Cells/Group	Aberrant Cells/Group (%)	Aberrations/ Group	Aberrations/ Cell (%)
0	2	0.4	2	0.004
75	3	0.5	5	0.008
250	2	0.3	3	0.005
750	0	0	0	0
PC	103	31.8	646	1.99
PC = positive control				

Reference: Monsanto Co. (1984). Hazleton Laboratories America Report HL-83-196, "*In Vivo* Bone Marrow Chromosome Study in Rats" (April 13).

Reliability: High because a scientifically defensible or guideline method was used.

Type: ***In vivo*** **Bone Marrow Chromosome Study in Mice**

Species/Strain: Mice/B6C3F_1

Sex/Number: Male and female/10 per sex per dose level

Route of Administration: Inhalation

Concentrations:	0, 1.6, 5, 16, 50, 160 mg HDDC/m^3
Method:	No specific test guideline was reported; however, a scientifically defensible approach was used to conduct the study. Mice were exposed to HDDC via inhalation 6 hours/day, 5 days/week for 13 weeks. Mice were 6-7 weeks of age when placed on study. At the end of the 13-week period, peripheral blood smears were prepared from samples obtained by cardiac puncture of all exposed and control mice. The slides were stained with Hoechst 33258/pyronin Y. Ten thousand normochromatic erythrocytes (NCE) and 2000 polychromatic erythrocytes (PCEs) from each animal were scored for micronuclei. Log transformation of the NCE data, and testing for normality by the Shapiro-Wilk test and for heterogeneity by Cochran's test were performed before statistical analyses. The frequency of micronucleated cells among NCEs was analyzed by analysis of variance using the SAS GLM procedure. The NCE data for each dose group were compared with the concurrent control group using Student's t-test. The frequency of micronucleated cells among PCEs was analyzed by the Cochran-Armitage trend test, and individual dose groups were compared to the concurrent control by Kastenbaum-Bowman's binomial test. The percentage of PCEs among total erythrocytes was analyzed by an analysis of variance on ranks (classed by sex) and individual dose groups were compared with the concurrent control using a t-test on ranks.
GLP:	Yes
Test Substance:	HDDC (1, 6-Hexanediamine dihydrochloride), purity 70%
Results:	Negative
Remarks:	No mortality occurred during the study, and there were no exposure-related changes in body weight. No significant increases were seen in the frequencies of micronucleated NCEs or PCEs in male or female mice. The percentage of PCEs among the total erythrocyte population was increased at the highest exposure levels for male and female mice.
Reference:	NTP (1993). Toxicity Report Series 24, NIH Publication 93-3347, "Technical Report on 1,6-Hexanediamine Dihydrochloride."
Reliability:	High because a scientifically defensible or guideline method was used.

Additional Reference for *In vivo* Genetic Toxicity: None Found.

APPENDIX B

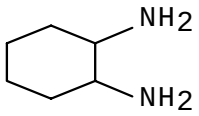
Existing published and unpublished data were collected and scientifically evaluated to determine the best possible study or studies to be summarized for each required endpoint. In the spirit of this voluntary program, other data of equal or lesser quality are not summarized, but are listed as related references at the end of each appropriate section, with a statement to reflect the reason why these studies were not summarized.

1.0 Substance Information

CAS Number: 694-83-7

Chemical Name: 1,2-Cyclohexanediamine

Structural Formula:



Other Names: 1,2-Diaminocyclohexane
Cyclohexanediamine
DACH
DCH
DCH-99
Diaminocyclohexane

Exposure Limits: 5 mg/m^3 (8- and 12-hour TWA): DuPont Acceptable Exposure Limit (AEL)

2.0 Physical/Chemical Properties

2.1 Melting Point

Value:	2°C (cis-isomer) 15°C (trans-isomer)
Decomposition:	No Data
Sublimation:	No Data
Pressure:	No Data
Method:	No Data
GLP:	Unknown
Reference:	DuPont Co. (1995). Material Safety Data Sheet No. DU005944 (June 28).
Reliability:	Not assignable because limited study information was available.

Additional References for Melting Point: None Found.

2.2 Boiling Point

Value:	191°C
Decomposition:	No Data
Pressure:	760 mm Hg
Method:	No Data
GLP:	Unknown
Reference:	DuPont Co. (1995). Material Safety Data Sheet No. DU005944 (June 28).
Reliability:	Not assignable because limited study information was available.

Additional References for Boiling Point: None Found.

2.3 Density

Value:	Specific gravity = 0.94
Temperature:	20°C
Method:	No Data
GLP:	Unknown
Results:	No additional data.
Reference:	DuPont Co. (1995). Material Safety Data Sheet No. DU005944 (June 28).
Reliability:	Not assignable because limited study information was available.

Additional References for Density: None Found.

2.4 Vapor Pressure

Value:	0.515 hPa (0.387 mm Hg)
Temperature:	20ºC
Decomposition:	No Data
Method:	No Data
GLP:	Unknown
Reference:	DuPont Co. (1974). Unpublished Data.
Reliability:	Not assignable because limited study information was available.

Additional References for Vapor Pressure: None Found.

Estimated by MPBPWIN v1.40 as 0.541 hPa. Calculated using MPBPWIN v1.40 as found in EPIWIN 3.05, Syracuse Research Company, Syracuse NY.

2.5 Partition Coefficient (log Kow)

Value:	0.09
Temperature:	25°C
Method:	Modeled. KOWWIN, v. 1.66, module of EPIWIN 3.05 (Syracuse Research Corporation). KOWWIN uses "fragment constant" methodologies to predict log P. In a "fragment constant" method, a structure is divided into fragments (atom or larger functional groups) and coefficient values of each fragment or group are summed together to yield the log P estimate.
GLP:	Not Applicable
Reference:	Meylan, W. M. and P. H. Howard (1995). J. Pharm. Sci., 84:83-92.
Reliability:	Estimated based on an accepted model.
Remark:	Generally, preference would be given to the experimental value for the Ko/w; however, since the partition coefficient is pH dependent the modeled parameter is used unless the pH of the experimental conditions was defined.

Additional Reference for Partition Coefficient (log Kow):

Leo, A. J. (1978). Report on the Calculation of Octanol/Water Log P Values for Structures in EPA Files (NISC/IS-0011845).

2.6 Water Solubility

Value:	904,400 mg/L
Temperature:	25°C
pH/pKa:	Estimated pKa: 9.9
Method:	Modeled. Solubility - WSKOWWIN v.1.40, module of EPIWIN v3.05 (Syracuse Research Corporation). Water solubility is estimated from log Kow using molecular weight and molecular fragment correction factors. pKa – SPARC on-line calculator, University of Georgia.
GLP:	Not Applicable
Reference:	Solubility - Meylan, W. M. et al. (1996). Environ. Toxicol. Chem., 15:100-106. pKa - http://ibmlc2.chem.uga.edu/sparc/index.cfm.
Reliability:	Estimated value based on accepted models.
Remark:	pH Dependency

Additional Reference for Water Solubility:

DuPont Co. (1995). Material Safety Data Sheet No. DU005944 (June 28).

2.7 Flash Point

Value:	75°C
Method:	Closed cup
GLP:	Unknown
Reference:	DuPont Co. (1995). Material Safety Data Sheet No. DU005944 (June 28).
Reliability:	Not assignable because limited study information was available.

Additional References for Flash Point: None Found.

2.8 Flammability: No Data.

3.0 Environmental Fate

3.1 Photodegradation:

Concentration:	No Data
Temperature:	No Data
Direct Photolysis:	Not expected to be susceptible to photolysis due to lack of chromophore structure for wavelengths ≥290 nm.
Indirect Photolysis:	AOP Program (v1.90) Results: ========== SMILES : C1(N)C(N)CCCC1 CHEM : 1,2-Cyclohexanediamine MOL FOR: C6 H14 N2 MOL WT : 114.19 ------- SUMMARY (AOP v1.90): HYDROXYL RADICALS ----- Hydrogen Abstraction = 60.2437×10^{-12} cm^3/molecule-sec Reaction with N, S and -OH = 42.0000×10^{-12} cm^3/molecule-sec Addition to Triple Bonds = 0.0000×10^{-12} cm^3/molecule-sec Addition to Olefinic Bonds = 0.0000×10^{-12} cm^3/molecule-sec Addition to Aromatic Rings = 0.0000×10^{-12} cm^3/molecule-sec Addition to Fused Rings = 0.0000×10^{-12} cm^3/molecule-sec OVERALL OH Rate Constant = 102.2437×10^{-12} cm^3/molecule-sec HALF-LIFE = 0.105 Days (12-hr day; 1.5×10^6 OH/cm^3) HALF-LIFE = 1.255 Hours As found in EPIWIN 3.05.
Breakdown Products:	No Data
Method:	Inspection of chemical structure

GLP:	Not Applicable
Reference:	Harris, J. C. (1990). Rate of Aqueous Photolysis, Chapter 8 In Lyman, W.J. et al. (eds.), Handbook of Chemical Property Estimation Methods, American Chemical Society, Washington, DC.
Reliability:	Estimate based on known qualitative structure-activity relationships.

Additional References for Photodegradation: None Found.

3.2 Stability in Water:

Concentration:	Not Applicable
Half-life:	Greater than 1 year
% Hydrolyzed:	Not Applicable
Method:	The stability of this material in water is estimated based on established chemical principles. Amines are considered resistant to hydrolysis by Harris, J. C. in Lyman W. et al. (1990). Handbook of Chemical Property Estimation Methods, page 7-6, American Chemical Society, Washington, DC. This indicates a hydrolytic half-life of greater than one year.
GLP:	Not Applicable
Reference:	Lyman W. et al. (1990). Handbook of Chemical Property Estimation Methods, page 7-6, American Chemical Society, Washington DC.
Reliability:	Estimate based on chemical principles.

Additional References for Stability in Water: None Found.

3.3 Transport (Fugacity):

Media:	Air, Water, Soil, and Sediments	
Distributions:	Air:	0.031%
	Water:	38.9%
	Soil:	61%
	Sediments:	0.072%
Half-life:	Air:	3.37 h
	Water:	360 h
	Soil:	720 h
	Sediments:	3240 h
Adsorption Coefficient:	Not Applicable	
Desorption:	Not Applicable	
Volatility:	Not Applicable	

Method:	Modeled. Calculated according to Mackay, Level III, Syracuse Research Corporation EPIWIN v3.05. Emissions (1000 kg/hr) to air, water, and soil compartments using standard EPA model defaults.
	Data Used: Molecular Weight: 114.19 Henry's Law Constant: 1.42e-9 atm-m^3/mole (HENRYWIN Program) Vapor Pressure: 0.407 mm Hg (MPBPWIN program) Liquid Vapor Pressure: 0.426 mm Hg (super-cooled) Melting Point: 27ºC (MPBPWIN program) Log Kow: 0.09 (KOWWIN program) Soil Koc: 0.504 (calc by model)
GLP:	Not Applicable
Reference:	Syracuse Research Corporation EPIWIN v3.05 contains a Level III fugacity model. The methodology and programming approach were developed by Dr. Donald MacKay and coworkers and are detailed in:
	Mackay, D. (1991). Multimedia Environmental Models: The Fugacity Approach, pp. 67-183, Lewis Publishers, CRC Press.
	Mackay, D. et al. (1996). Environ. Toxicol. Chem., 15(9):1618-1626.
	Mackay, D. et al. (1996). Environ. Toxicol. Chem., 15(9):1627-1637.
Reliability:	Estimated value based on accepted model.

Additional References for Transport (Fugacity): None Found.

3.4 Biodegradation

Value:	The theoretical oxygen demand (ThOD) was calculated as 3.96 mg O_2/mg test substance.
	For the test substance, the following biodegradability was found: 0% after 7 days, 46% after 14 days, 101% after 17 days, 21 days, and 28 days.
	Additional nitrate measurements of the 28-day samples confirmed a total nitrification of the test substance during the

	test period. Therefore, the test substance was classified as ready biodegradable according to the Guidelines.
Breakdown Products:	No Data
Method:	The biochemical degradability of the test substance at 293 K (20ºC) was determined based on the recommendations of the following guideline: OECD Guideline No. 301 D (which corresponds to the EC-Method, Part C.4, Part E): "Ready Biodegradability: Closed Bottle Test". The mineral nutrient solution was prepared according to the prescriptions of the Guideline, the inoculum was a composite made from equal parts of the total effluent and the reflux of an activated sludge plant. The oxygen depletion was measured after 7, 14, 17, 21, and 28 days by means of an oxygen electrode. Control- and blank-series without test substance were run simultaneously and the effectiveness of the inoculum was confirmed (in a third series with sodium acetate as the reference substance) and found to be 102% after 28 days under the conditions of the test.
GLP:	Yes
Reference:	DuPont Co. (1997). Unpublished Data, NATEC Institut Study No. 969410/1.2, "Biochemical Degradability: Test Substance DCH 99% Polyamine" (June 4).
Reliability:	High because a scientifically defensible or guideline method was used.

Additional References for Biodegradation: None Found.

3.5 Bioconcentration:

Value:	BCF 3.162 (estimated)
Method:	Modeled. BCFWIN, v. 2.14
GLP:	Not Applicable
Reference:	The estimation methodology used by BCFWIN is described in the following document prepared for the U.S. Environmental Protection Agency (OPPT): "Improved Method for Estimating Bioconcentration Factor (BCF) from Octanol-Water Partition Coefficient," SRC TR-97-006 (2nd Update), July 22, 1997; prepared for Robert S. Boethling, EPA-OPPT, Washington, DC; Contract No. 68-D5-00012; prepared by William M. Meylan, Philip H. Howard, Dallas Aronson, Heather Printup, and Sybil Gouchie; Syracuse Research Corp., Environmental Science Center, 6225 Running Ridge Road, North Syracuse, NY 13212.

Reliability: Estimated value based on accepted model.

Additional References for Bioconcentration: None Found.

4.0 Ecotoxicity

4.1 Acute Toxicity to Fish

Type:	**48-hour LC_{50}**
Species:	Orfe, *Leuciscus idus melanotus*
Value:	200 mg/L
Method:	The procedure used in the test was based on the recommendations of the following guideline: German Standard "Deutsches Einheitsverfahren" DIN 38 412, Part 15.

The effects of the test substance on *Leuciscus idus melanotus* within 48 hours were examined and compared to a negative control. Ten fish were exposed to various concentrations of the test substance (0, 100, 180, 320, and 580 mg/L) in water without using any solubilising agent. The test was performed using a static test procedure. Two hours before test start, 15 L of each concentration were prepared and distributed in the test containers. These solutions were stored under test conditions until the test started. After this precoating time, the solutions were replaced by freshly prepared solutions and 10 animals were introduced into the test containers (1 test container for each concentration).

The main test criteria were the mortalities after 24 and 48 hours in each solution. Those animals showing no reaction within a few seconds after touching the caudal peduncle were considered to be dead. Dead animals were removed at the observation times and test containers were exchanged and cleaned. Other significant effects compared to the control observed in the test containers were also documented.

Ambient air was pumped by means of an aquarium aerator through silicon rubber tubes and "flow-out stones" into the aquaria. The air flow was adjusted in order to maintain an oxygen concentration of >80% of the saturation. No feeding occurred during the test. Sixteen hours of light and 8 hours of darkness were provided during the test. Water hardness was 2.2 mole $CaCO_3$/L. Oxygen concentration, pH, and temperature were recorded at 0.1, 24, and 48 hours.

GLP:	Yes
Test Substance:	1,2-Cyclohexanediamine, purity >99 % wt.
Results:	After evaluation of the results with a "Probit" method, the following toxicity data were obtained: NOEC = 100 mg/L (nominal); 0% mortality at 100 mg/L (nominal); LC_{50} = 200 mg/L (nominal); 100% mortality = 320 mg/L (nominal). No other effects of the test substance in the test containers compared to the control were observed. The pH was 8.4 when measured at 0.1, 24, and 48 hours. The oxygen content (% of saturation) was 92, 92, and 93 at 0.1, 24, and 48 hours, respectively. The water temperature was 20.1, 20.2, and 20.2ºC at 0.1, 24, and 48 hours, respectively.
Reference:	DuPont Co. (1997). Unpublished Data, NATEC Institut Study No. 969410/1.3, "Acute Toxicity Test on the Orfe (*Leuciscus idus melanotus*) Static Test Procedure, 48 Hours" (June 3).
Reliability:	Medium because a suboptimal study design (nominal concentrations and 48-hours) was used for testing.

Type:	**96-hour LC_{50}**
Species:	Freshwater fish
Value:	525 mg/L
Method:	Modeled, ECOSAR (using log Kow of 0.09)
GLP:	Not Applicable
Test Substance:	1,2-Cyclohexanediamine
Results:	No additional data.
Reference:	Meylan, W. M. and P. H. Howard (1999). User's Guide for the ECOSAR Class Program, Version 0.993 (Mar 99), prepared for J. Vincent Nabholz and Gordon Cas, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics, Washington, DC, prepared by Syracuse Research Corp., Environmental Science Center, Syracuse, NY 13210 (submitted for publication).
Reliability:	Estimated value based on accepted model.

Additional References for Acute Toxicity to Fish: None Found.

4.2 Acute Toxicity to Invertebrates:

Type:	**48-hour EC_{50}**

Species:	Daphnid
Value:	30.3 mg/L
Method:	Modeled, ECOSAR (using $\log_{10}$ Kow of 0.09)
GLP:	Not Applicable
Test Substance:	1,2-Cyclohexanediamine
Results:	No additional data.
Reference:	Meylan, W. M. and P. H. Howard (1999). User's Guide for the ECOSAR Class Program, Version 0.993 (Mar 99), prepared for J. Vincent Nabholz and Gordon Cas, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics, Washington, DC, prepared by Syracuse Research Corp., Environmental Science Center, Syracuse, NY 13210 (submitted for publication).
Reliability:	Estimated value based on accepted model.

Additional References for Acute Toxicity to Invertebrates: None Found.

4.3 Acute Toxicity to Aquatic Plants:

Type:	**96-hour EC_{50}**
Species:	Green algae
Value:	29.6 mg/L
Method:	Modeled, ECOSAR (using $\log_{10}$ Kow of 0.09)
GLP:	Not Applicable
Test Substance:	1,2-Cyclohexanediamine
Results:	No Data
Reference:	Meylan, W. M. and P. H. Howard (1999). User's Guide for the ECOSAR Class Program, Version 0.993 (Mar 99), prepared for J. Vincent Nabholz and Gordon Cas, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics, Washington, DC, prepared by Syracuse Research Corp., Environmental Science Center, Syracuse, NY 13210 (submitted for publication).
Reliability:	Estimated value based on accepted model.

Additional References for Acute Toxicity to Aquatic Plants: None Found.

5.0 Mammalian Toxicity

5.1 Acute Toxicity

Oral Study No. 1: Data for DCH

Type:	**Oral ALD**
Species/Strain:	Male rats/Crl:CD®BR
Value:	2300 mg/kg
Method:	No specific test guideline was reported; however, a

scientifically defensible approach was used to conduct the study.

Male rats, approximately 8 weeks old at study start, were administered 450, 670, 1000, 1500, 2300, or 3400 mg/kg of the test substance in distilled water as a single dose by intragastric intubation. Each test group consisted of 1 male rat. Following administration of the test substance, rats were observed for clinical signs of toxicity. Surviving rats were weighed and observed for clinical signs daily until signs of toxicity subsided, and then at least 3 times/week throughout the 14-day post-exposure period. Observations for mortality were conducted daily. No animal necropsies were performed at the conclusion of the post-exposure period.

GLP: Yes

Test Substance: 1,2-Diaminocyclohexane, purity 89%

Results: Mortality occurred in the 1000, 2300, and 3400 mg/kg groups. However, clinical signs of toxicity indicative of a dosing injury were observed in the 1000 mg/kg rat after dosing. These included dry red nasal and oral discharge 1 day after dosing, lung noise on post-dosing days 3 and 4, lung noise and gasping on day 7, and death on day 8. Since the rat dosed at 1500 mg/kg did not exhibit these clinical signs and survived the 14-day observation period, the death at 1000 mg/kg was attributed to a dosing injury or animal variability.

No clinical signs of toxicity attributed to the test substance were observed in the rats dosed at 450 or 670 mg/kg. The rat dosed at 1500 mg/kg exhibited lethargic behavior and red nasal discharge 1 day after dosing. The rats dosed at 2300 or 3400 mg/kg exhibited lethargic behavior, red nasal discharge, salivation or red oral discharge, and prostrate posture approximately 1 hour after dosing and were found dead 1 day after dosing.

The rats dosed at 670 or 1500 mg/kg had slight weight loss (up to 5% of initial body weight) one day after dosing. Severe weight loss (20% of initial body weight) was observed in the rat dosed at 1000 mg/kg 2 days after dosing and weight loss persisted until the animal's death.

Reference: DuPont Co. (1988). Unpublished Data, Haskell Laboratory Report No. 761-88, "Approximate Lethal Dose (ALD) of 1,2-Cyclohexanediamine in Rats" (December 7).

Reliability: High because a scientifically defensible or guideline method was used.

Oral Study No. 2: Data for Mixture containing HMD, DCH, and MPMD

Type:	**Oral LD_{50}**
Species/Strain:	Male and Female rats/Sprague Dawley
Value:	1100 mg/kg
Method:	No specific test guideline was reported; however, a scientifically defensible approach was used to conduct the study. Single oral dose of undiluted test material was administered to 5 rats per dose group. Dose levels were 794 (3 males/2 females), 1000 (2 males/3 females), 1260 (3 males/2 females), and 1580 (2 males/3 females) mg/kg. Animals were monitored for clinical signs and body weight over a 14-day period. Gross pathological evaluations were conducted at study termination and on animals dying on study.
GLP:	No Data
Test Substance:	Amines Heads, purity not specified (HMD Purge stream) Exact composition data not provided. Based on other analytical data, this purge stream typically contains.

HMD	30-50%
1,4-Butanediamine	20-40%
MPMD	5-10%
DCH	5-10%
Water	5-15%
Other Diamines	1-5%

Results:	Mortality was observed at all dose levels. Mortality incidence for the treated groups was as follows: 1 (1 female)/5, 794 mg/kg; 2 (1 male/1 female)/5, 1000 mg/kg; 3 (1 male/2 female)/5, 1260 mg/kg; 5/5 1580 mg/kg. Deaths occurred from 1 to 6 days post treatment. Clinical signs included reduced appetite and activity (lasting from 2 to 7 days in survivors), increasing weakness, diarrhea, collapse, and death. Gross necropsy of animals expiring on study included hemorrhagic lungs, liver hyperemia, and acute gastrointestinal inflammation. Indication of blood and feed in the abdominal cavity was noted in some instances. Terminal sacrifice indicated lung hyperemia and acute gastrointestinal inflammation in some instances. Distended viscera was observed in some instances.
Reference:	Solutia Inc. (1977). Unpublished Data, Report No. YO 770168, "Toxicity Studies on Amine Heads (Decatur HMD Purge Stream)" (July 27).
Reliability:	High because a scientifically defensible or guideline method was used.

Additional References for Acute Oral Toxicity:

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

DuPont Co. (1974). Unpublished Data, Haskell Laboratory Report No. 379-74, "Acute Oral Test" (July 9).

Stephan Co. (1977). Industrial Biotest Laboratory Report IBT No. 8530-10884, "Acute Oral Toxicity Study in Albino Rats" (October 24) (TSCA Fiche OTS0535386 and OTS0535386-1).

Inhalation Data for DCH

Type:	**Inhalation ALC**
Species/Strain:	Male rats/Crl:CD®BR
Exposure Time:	4 hours
Value:	3.2 mg/L (for the 98% pure material)
Method:	No specific test guideline was reported; however, a scientifically defensible approach was used to conduct the study. Groups of either 6 or 10 male rats were exposed for a single 4-hour period to atmospheres containing DCH vapor and aerosol in air. Three different purities of DCH were tested: 89, 93, and 98%. Four different batches of DCH were used, 2 of higher purity (98%) and two of the lower purities (89 and 93%). Rats were approximately 7 or 8 weeks old and weighed between 239 and 300 grams on the day of the exposures. Except during exposure, food and water were available *ad libitum*. Animal rooms were maintained on a timer-controlled, 12 hour/12 hour light/dark cycle. Environmental conditions of the animal rooms were targeted for a temperature of 23±2°C and relative humidity of 50±10%. Any excursions outside these ranges were of small magnitude and/or brief duration and did not adversely affect the validity of the study. In addition to determining the ALC of the test material, the effect of DCH purity on toxicity, the effects of two different atmosphere generation techniques, and the effects of toxicity of DCH atmosphere generation under nitrogen or air were evaluated. Test atmospheres of DCH were generated by evaporation of

the heated test material under air or nitrogen. Because of the changes in test samples and equipment, the study was conducted in 2 phases separated by about 1.5 years.

In the 1st phase, a heated round bottom flask was used to vaporize the 89% DCH or 98% DCH. Aerosol and vapor atmospheres were generated by metering the test material with a infusion pump to an Instatherm Flask heated to 124-149°C. Air introduced at the flask swept the aerosol/vapor mixture into a glass transfer tube, where dilution air was added. The generation system for the second exposure to 98% DCH was identical except that nitrogen swept the aerosol/vapor mixture to the transfer tube instead of air. The DCH mixture then discharged directly into a 38-L cylindrical glass exposure chamber and was dispersed with a baffle to promote uniform chamber distribution. Chamber concentrations were controlled by varying the test material feed rates into the flask.

In the 2nd phase a J-tube and heated air were used to vaporize the 93% DCH or 98% DCH. Aerosol and vapor concentrations were generated by pumping DCH with an infusion pump to a glass J-tube containing 6 mm glass beads. An electronic torch heated the air entering the J-tube. The torch temperature was controlled by a temperature controller. The temperature entering the J-tube ranged from 60-82°C, and the temperature exiting the J-tube ranged from 42-62°C. The DCH aerosol/vapor mixture then discharged directly into a 29-L cylindrical glass exposure chamber and was dispersed with a baffle to promote uniform chamber distribution. Chamber concentrations of DCH were controlled by varying the test material feed rates into the J-tube.

The vapor portion of the atmosphere was analyzed using gas chromatography and the aerosol portion measured gravimetrically. In the 1st testing phase, chamber temperatures were measured with mercury thermometers, chamber relative humidity was measured with a pyschometer, and chamber oxygen concentration was measured with an oxygen monitor. In the 2nd testing phase, chamber temperatures were measured with thermocouples, chamber relative humidity was measured with a pyschometer, and chamber oxygen concentration was measured with an oxygen monitor.

The atmospheric particulate concentration of DCH was calculated from the pre- and post-sampling filter weights, which were determined with an automatic electrobalance. Airborne particle size was determined with a cascade impactor.

Rats were individually restrained in perforated stainless steel or polycarbonate cylinders with conical nose pieces. Each restrainer was inserted into face plated on 29- or 38-L glass exposure chambers such that only the nose of the each rat extended into the chamber. Rats were weighed prior to exposure and were observed for clinical signs of toxicity during exposure in the second phase. In the first testing phase, rats could not be seen during exposure due to a thick coating of the test material on the chamber walls. In all but 1 exposure, rats were observed for clinical signs of toxicity upon being released from their restrainers after the exposure. Rats were weighed and observed for clinical signs of toxicity during a 14- or 15-day recovery period.

GLP: Yes

Test Substance: 1,2-Diaminocyclohexane, purity 89, 93, and 98%

Results: All chamber oxygen measurements were 21%. In the 1st phase, chamber temperatures ranged from 28-32°C and chamber relative humidity ranged from 69-82%. In the 2nd phase, chamber temperatures ranged from 24-29°C and chamber relative humidity ranged from 26-29%.

The following table summarizes mortality data.

% DCH	Mean Total DCH (mg/L)	Mortality # deaths/# exposed	Aerosol Particle Size (MMD)[c]	Aerosol Particle Size (% <10 μm)[d]
98[a]	4.73	0/10	3.4	88
98[ae]	3.34	0/10	5.6	81
89[a]	3.09	0/10	4.0	84
93[b]	3.30	0/6	7.6	65
98[b]	3.23	1/6	9.5	55

[a] = Testing phase 1 (round bottom flask)
[b] = Testing phase 2 (J-tube)
[c] = Mass median aerodynamic diameter in micrometers
[d] = Percent by weight of particles with aerodynamic diameter less than 10 μm
[e] = Nitrogen was used in this exposure as the generation gas instead of air

Rats in the 1st testing phase showed slight to severe weight loss after exposure, and resumed a normal weight gain rate from 2 to 4 days after exposure. In the 2nd testing phase, rats exposed to 93% DCH showed moderate to severe weight loss after exposure, but resumed a normal weight gain rate by the 3rd day after exposure. Rats exposed to 98% DCH had severe weight loss after exposure, but rats which ultimately survived resumed a normal weight gain rate by the 4th day after exposure, with transient episodes of weight loss. Slight weight loss was defined as < 10 grams, moderate weight loss was 10-20 grams, and severe weight loss was > 20 grams.

In the 1st testing phase, immediately following exposure, rats from all groups showed red nasal and ocular discharges, hunched posture, and compound-stained feces. In addition, rats exposed to the highest total concentration had partially closed eyes. During the recovery period, commonly seen clinical signs were clear or red ocular discharge, red discharge around the nose and mouth, brown nasal discharge, stained or wet perineum, and compound-stained faces.

In the 2nd testing phase, immediately following exposure, rats from the 93% DCH group had compound-stained faces, red nasal and ocular discharges, and some showed small red sores on the nose and ears and slight transient tremors. The slight transient tremors observed briefly in 3 of 6 rats after a single experiment were fleeting and considered not directly compound-related and may have been due to physical restraint or environmental factors concurrent with the effects of near-lethal exposure to DCH. During the recovery period, common clinical signs observed in rats from both exposure groups (93 and 98%) were: sores on the face, ears, and front feet, dry red nasal and ocular discharges, dry brown discharge around the mouth, partially closed eyes, yellow or brown stained perineum, compound-stained or discolored (red) fur, hair loss on the face, labored breathing, lung noise, gasping, and lethargy. Some of these clinical signs were observed throughout the recovery period in some rats, but generally speaking the frequency and severity of the clinical signs decreased throughout the recovery period.

Under the conditions of this study, an LC_{50} could not be determined, however, the ALC for 98% DCH was

determined to be 3.2 mg/L (combined aerosol and vapor mean concentrations). One of the 6 rats in this exposure group was found dead on the 4th day after exposure. No deaths occurred in the groups exposed to the 89 or 93% DCH at concentrations greater than 3 mg/L.

Of 5 exposures conducted with DCH formulations at concentrations > 3 mg/L, only one exposure produced lethality in rats. In this exposure, a 98% formulation was tested using a J-tube to generate the test atmosphere. Although other exposures produced atmospheres containing higher DCH concentrations (combined aerosol/vapor), the lethal exposure atmosphere contained more vapor and less aerosol than the other experiments.

Reference: DuPont Co. (1993). Unpublished Data, Haskell Laboratory Report No. 554-93, "Four-Hour Inhalation Lethality Studies with 1,2-Diaminocyclohexane in Rats" (November 2).

Kelly, D. P. et al. (1992). The Toxicologist, 12(1):357 (Abstract 1399).

Reliability: High because a scientifically defensible or guideline method was used.

Additional References for Acute Inhalation Toxicity: None Found.

Dermal Study No. 1: Data for a mixture containing HMD and DCH

Type: **Dermal ALD**

Species/Strain: Male rabbits/albino

Exposure Time: 24 hours

Value: 7500 mg/kg

Method: No specific test guideline was reported; however, a scientifically defensible approach was used to conduct the study.

Adult male rabbits were clipped free of hair over the back and trunk area and fitted with plastic collars. Undiluted test material was applied to the back of each rabbit under gauze pads. The trunk of each rabbit was then wrapped with a layer of Saran® wrap, gauze bandage, and adhesive tape. Dose levels of 3400 (1 rabbit), 5000 (1 rabbit), 7500 (1 rabbit), and 10,000 mg/kg (2 rabbits) were tested. After a 24-hour period, the wrappings were removed and the treated site was washed with water and dried. Surviving animals were observed for 14 days before being sacrificed.

GLP: No

Test Substance: 1,6-Hexanediamine/1,2-Diaminocyclohexane

(69.5%/30.5%)

Results: The treated rabbits showed only mild systemic signs (lethargy, hyperactivity, and weakness) with death within 2 days at 7500 mg/kg and above. The rabbit treated with 5000 mg/kg was lethargic for 24 hours after treatment and experienced weight loss for 9 days after treatment. The rabbit treated with 3400 mg/kg experienced weight loss for 7 days after treatment.

The test material produced severe skin irritation with necrosis within 24 hours after treatment.

Reference: DuPont Co. (1974). Unpublished Data, Haskell Laboratory Report No. 720-74, "Acute Skin Absorption Test" (December 17) (also cited in TSCA Fiche OTS0571406).

Reliability: High because a scientifically defensible or guideline method was used.

Dermal Study No. 2: Data for a mixture containing HMD, DCH, and MPMD

Type: **Dermal LD_{50}**

Species/Strain: Male and female rabbits/New Zealand White

Exposure Time: 24 hours

Value: > 501-794 mg/kg

Method: No specific test guideline was reported; however, a scientifically defensible approach was used to conduct the study.

One undiluted application of test substance was applied to skin of albino rabbits at dose levels of 316, 501, 794, 1260, 2000 mg/kg, 1 rabbit per dose level. Application was covered with a semi-occlusive patch with exposure lasting 24 hours. Rabbits were evaluated daily for clinical signs and body weight. Gross necropsy was conducted on animals expiring on study and on surviving animals at study termination (day 14 post exposure).

GLP: No Data

Test Substance: Amines heads ("HMD Purge Stream") mixture

Exact composition data not provided. Based on other analytical data, this purge stream typically contains.

HMD	30-50%
1,4-Butanediamine	20-40%
MPMD	5-10%
DCH	5-10%
Water	5-15%
Other Diamines	1-5%

Results: Rabbits in the 794, 1260, and 2000 mg/kg treatment groups died prior to study termination. Rabbits in the 316 and

	501 mg/kg treatment groups survived for the duration of the post treatment period. Observations included reduced appetite and activity (3 to 5 days in survivors), increasing weakness, collapse, and death. Gross necropsy in animals expiring during the course of the study revealed lung hyperemia, liver discoloration (blanched), spleen discoloration, and kidney blanching. Animals appeared cyanotic. Viscera appeared normal in animals sacrificed at study termination.
Reference:	Solutia Inc. (1977). Unpublished Data, Report No. YO 770168, "Toxicity Studies on Amine Heads (Decatur HMD Purge Stream)" (July 27).
Reliability:	Medium because a suboptimal study design was used.

Additional References for Acute Dermal Toxicity: None Found.

Dermal Irritation Study for DCH

Type:	**Dermal Irritation**
Species/Strain:	Female rabbits/New Zealand white
Method:	No specific test guideline was reported; however, a scientifically defensible approach was used to conduct the study. On the day prior to study initiation, the hair of 6 rabbits was closely clipped to expose the back from the scapular to the lumbar region. The rabbits weighed from 2584 to 2906 grams on the day of treatment. Each rabbit was placed in a stock. A 0.5 mL aliquot of the test material was applied directly on the test site beneath a 2-inch gauze square that was held in place with tape. Rubber sheeting was then wrapped around the animal and secured with clips to retard evaporation and to keep the test material in contact with the skin without undue pressure. Approximately 24 hours after application of the test material, the rubber sheeting was loosened, and the skin at the corners of the gauze squares was marked with a waterproof pen, wrappings and gauze squares were then removed. The test sites were gently washed with warm water to remove excess test material and the skin was gently patted dry and the rabbits were returned to their cages. Approximately 24 and 48 hours after application of the test material, the test sites were evaluated for erythema, edema, and other evidence of dermal effects. Each test site was scored according to the Draize scale. The adjacent areas of untreated skin were used for comparison.
GLP:	Yes
Test Substance:	1,2-Diaminocyclohexane, purity 89%

Results:	DCH produced severe erythema with necrosis in all of the treated rabbits throughout the 48-hour study. Moderate to severe edema was observed in all of the rabbits by 24 hours after treatment. By 48 hours, moderate edema was observed in all of the rabbits. DCH was considered a severe skin irritant.
Reference:	DuPont Co. (1988). Unpublished Data, Haskell Laboratory Report No. 725-88, "Skin Irritation Test in Rabbits of 1,2-Cyclohexanediamine" (November 7). Brock, W. J. (1990). Acute Toxic Data, 1(1):8-9 (RTECS/GU8749500).
Reliability:	High because a scientifically defensible or guideline method was used.

Additional References for Dermal Irritation:

Data from this additional source support the study results summarized above. This study was not chosen for detailed summarization because the data were not substantially additive to the database.

DuPont Co. (1989). Unpublished Data, Haskell Laboratory Report No. 819-88, "Dermal Sensitization Study with 1,2-Cyclohexanediamine in Guinea Pigs" (January 3).

Solutia Inc. (1977). Unpublished Data, Report No. YO 770168, "Toxicity Studies on Amine Heads (Decatur HMD Purge Stream)" (July 27).

DuPont Co. (1974). Unpublished Data, Haskell Laboratory Report No. 657-74, "Department of Transportation Skin Corrosion Test on Rabbit Skin" (November 26).

Dermal Sensitization Study for DCH

Type:	**Dermal Sensitization**
Species/Strain:	Guinea pigs/Duncan Hartley albino
Method:	No specific test guideline was reported; however, a scientifically defensible approach was used to conduct the study. A rangefinding study was conducted on 1 male and 2 female guinea pigs. Aliquots (approximately 0.05 mL) of 100% (the neat test material), 50%, 25%, and 10% (v/v) emulsions of the test material in distilled water were applied and lightly rubbed onto separate test sites on the shaved, intact skin of each guinea pig's back. Irritation responses were scored approximately 24 and 48 hours after treatment.

The primary irritation phase was conducted in 10 guinea pigs (5 male and 5 female), weighing 441 to 570 grams, by applying and lightly rubbing in 1 drop (approximately 0.05 mL) of 10% and 1% (v/v) emulsions of the test material in distilled water onto separate sites of shaved, intact skin of each guinea pig. Five vehicle control guinea pigs (3 male and 2 female), weighing 474 to 589 grams, were also treated by applying and lightly rubbing in 1 drop (approximately 0.05 mL) of distilled water onto separate sites of shaved, intact skin of each guinea pig. In addition 10 positive control guinea pigs (5 male and 5 female), weighing 423 to 614 grams, were treated by applying and lightly rubbing in 1 drop of 30% and 3% (w/v) suspensions of p-phenylenediamine in acetone:dimethyl phthalate (1:9 ratio) onto separate sites of shaved, intact shoulder skin of each guinea pig. Dermal responses were scored approximately 24 and 48 hours after application of the test material.

Two days after the primary dermal application phase, the induction phase of the study was initiated using the same test guinea pigs. Induction consisted of a series of 4 sacral intradermal injections (1 each week) of 0.1 mL of a 1.0% (v/v) emulsion of DCH in physiologic saline. The same injection procedure was followed for the 5 vehicle control guinea pigs using physiologic saline and for the 10 positive control guinea pigs using 0.1 mL of a 1.0% (w/v) suspension of p-phenylenediamine in acetone:dimethyl phthalate (1:9 v/v). Skin responses were evaluated approximately 24 hours after each injection.

Two weeks after the last induction treatment, the test guinea pigs were challenged for sensitization by applying and lightly rubbing in 1 drop (approximately 0.05 mL) of 10% and 1% (v/v) emulsions of the test material in distilled water onto separate sites of shaved, intact shoulder skin. The 5 vehicle control guinea pigs received identical topical applications of the distilled water. The positive control guinea pigs were challenged for sensitization by applying and lightly rubbing in 1 drop of 30% and 3% (w/v) suspensions of p-phenylendiamine in acetone:dimethyl phthalate (1:9) onto separate sites of shaved, intact skin. Also 2 male and 3 female guinea pigs, weighing between 402 to 587 grams at study initiation, were treated by applying 1 drop of 10% and 1% (v/v) emulsions of the test substance in distilled water and 1 drop of the vehicle

(distilled water) onto separate sites of shaved, intact skin. A second group of 2 male and 3 female guinea pigs, weighing 422 to 511 grams, were treated by applying 1 drop of 30% and 3% (w/v) suspensions of the positive control material onto separate sites of shaved, intact skin. These 2 groups of guinea pigs served as negative control animals.

Approximately 1 week following challenge, the test guinea pigs were rechallenged for sensitization. The guinea pigs were treated with the test material in the same manner as described for the challenge phase. In addition, a naive group of 3 male and 2 female guinea pigs, weighing 545 to 800 grams, served as another group of negative control animals. The positive control and vehicle control animals were not rechallenged. Responses were scored approximately 24 and 48 hours after application of the test material.

GLP: Yes

Test Substance: 1,2-Diaminocyclohexane, purity 89%

Results: In the rangefinding test, severe erythema with necrosis was observed in the 100 and 50% concentration sites. Mild or severe erythema with necrosis was observed in the 25% concentration sites. No or slight erythema was observed at the 10% concentration sites. Based on the results of the rangefinding test, 10% and 1% concentrations were used for the main study.

During the primary irritation phase, slight erythema was observed in 3 animals at 24 hours and in 1 animal at 48 hours after treatment with the 10% concentration. No dermal irritation was observed in the 1% concentration sites, vehicle control, or positive control animals.

During the induction phase, severe erythema with necrosis, superficial necrosis, or blanching was observed in the test guinea pigs. One guinea pig was found dead prior to the 4^{th} induction treatment. A cause of death for this animal could not be determined. No dermal irritation was observed in the vehicle control animals. Blanching and necrosis were also observed in the positive control animals.

At 24 and 48 hours following challenge, moderate erythema was observed in 3 guinea pigs, and slight or mild erythema was observed in 5 guinea pigs in the 10% concentration sites. Slight erythema was observed in 3 negative control animals treated with a 10% emulsion of the test material.

Eschar was observed in 2 guinea pigs. No dermal irritation was observed in the 1% concentration sites of the test or negative control animals. Based on the dermal irritation seen in the 10% concentration level, the results suggest that DCH was a weak dermal sensitizer. To confirm these results, the test animals were rechallenged. A weak dermal irritation response was obtained by 24 and 48 hours following rechallenge with the 10% emulation of DCH. Mild or moderate erythema was observed in 2 guinea pigs, and no or slight erythema was observed in the other guinea pigs. No dermal irritation was observed at the 1% concentration level, or in negative controls treated with 10% or 1% of the test material.

In the positive control animals, slight to moderate erythema was observed in the 30% concentration sites following challenge. Slight or mild erythema was observed in the 3% concentration sites.

Reference: DuPont Co. (1989). Unpublished Data, Haskell Laboratory Report No. 819-88, "Dermal Sensitization Study with 1,2-Cyclohexanediamine in Guinea Pigs" (January 3).

Brock, W. J. (1990). Acute Toxic Data, 1(1):8-9 (RTECS/GU8749500).

Reliability: High because a scientifically defensible or guideline method was used.

Additional Reference for Dermal Sensitization:

Data from this additional source support the study results summarized above. This study was not chosen for detailed summarization because the data were not substantially additive to the database.

Kirkup, M. E. et al. (2001). Contact Dermatitis, 45(2):121-122.

Eye Irritation Study for a mixture containing HMD and DCH

Type: **Eye Irritation**

Species/Strain: Rabbit/Albino

Method: No specific test guideline was reported; however, a scientifically defensible approach was used to conduct the study.

0.1 mL of the undiluted test substance was placed into the right conjunctival sac of each of 2 albino rabbits. After 20 seconds, 1 treated eye was washed with tap water for 1 minute. The treated eye of the other rabbit was not

	washed. Observations of the cornea, iris, and conjunctiva were made with a hand-slit lamp at 1 and 4 hours, and at 1, 2, 3, 7, and 14 days. A 5% aqueous fluorescein stain and a biomicroscope were used at the examinations after the day of treatment.
GLP:	No
Test Substance:	1,6-Hexanediamine/1,2-Diaminocyclohexane (69.5%/30.5%)
Results:	The test substance produced severe, irreversible corneal opacity, moderate iritis, severe conjunctivitis, and necrosis of the eyelids. At 7 days, the eye dosed and not washed was completely closed with a purulent discharge. The eye was forced open, washed out, and the eye did not react to light. The rabbit was sacrificed at this time. The eye dosed with the test substance and promptly washed had generalized moderate opacity, moderate iritis, and severe conjunctivitis. At 14 days the cornea appeared to be healing, conjunctivitis was mild, but the moderate iritis persisted.
Reference:	DuPont Co. (1974). Unpublished Data, Haskell Laboratory Report No. 658-74, "Eye Irritation Test in Rabbits" (November 26).
Reliability:	High because a scientifically defensible or guideline method was used.

Additional Reference for Eye Irritation:

Data from this additional source support the study results summarized above. This study was not chosen for detailed summarization because the data were not substantially additive to the database.

Solutia Inc. (1977). Unpublished Data, Report No. YO 770168, "Toxicity Studies on Amine Heads (Decatur HMD Purge Stream)" (July 27).

5.2 Repeated Dose Toxicity

Repeated Dose Study No. 1: Data for DCH

Type:	**2-Week Inhalation Toxicity Test**
Species/Strain:	Rats/Crl:CD®BR
Sex/Number:	Male/10 per exposure level
Exposure Period:	2 weeks
Frequency of Treatment:	6 hours/day, 5 days/week
Exposure Levels:	0, 10, 50, 250 mg/m^3

Method: No specific test guideline was reported; however, a scientifically defensible approach was used to conduct the study.

Three test groups were exposed nose-only, to aerosol/vapor mixtures of DCH in air at design concentrations of 10, 50, or 250 mg/m^3. A control group of age-and weight-matched rats was exposed simultaneously to air only. Rats were exposed 6 hours/day, 5 days/week for 2 weeks, and 5/10 rats per group were retained for a 14-day post-exposure recovery period. Atmospheres containing aerosol and vapor DCH were generated by pumping the test material with an infusion pump to a glass J-tube containing 6 mm beads. An electronic torch heated the air entering the J-tube to about 60-70ºC. The torch temperature was controlled by a temperature controller. The aerosol/vapor mixture entered the chamber and was dispersed by a glass baffle to promote uniform distribution of the test material throughout the exposure chamber. The exposure chambers were monitored approximately hourly for DCH during the exposures and analyzed via gas chromatography. Airborne particle size was determined weekly for each exposure concentration with a cascade impactor. Chamber temperatures were measured continually with thermocouples during each exposure and recorded hourly. Relative humidity was measured twice per exposure with a psychrometer and chamber oxygen was measured twice per exposure with an oxygen monitor.

Rats were individually restrained in either perforated stainless steel or polycarbonate cylinders with conical nose pieces. Each restrainer was inserted into face plates on glass 29-L chambers such that only the nose extended into the exposure chamber.

During the exposure period, all rats were weighed and observed for clinical signs prior to each exposure and on the weekend between the exposure weeks. Clinical signs were observed during and immediately after each exposure. During the recovery period, all rats were weighed and observed for clinical signs daily excluding weekends.

Urine samples were collected from each rat after the 9^{th} exposure, and from the remaining 5 rats/group on the 13^{th} day of recovery. Samples were analyzed for approximately 12 parameters.

Blood samples were taken from all rats after the 10th exposure, and from the remaining 5 rats/group on the 14th day of recovery. Twelve hematological and 15 clinical chemistry parameters were measured or calculated.

Each test group of 10 rats was divided into subgroups of 5 rats. The first 5 rats per group were killed after the 10th exposure, and the remaining rats in each group were killed on the 14th day of recovery for gross and histopathologic examinations. Gross examinations were conducted on all rats, and 30 tissues were saved for microscopic examination. Organ weights were recorded for 5 of the organs (liver, brain, kidneys, lungs, and testes).

Mean body weights and body weight gains were analyzed by one-way analysis of variance. Exposure group values were compared to controls by the least significant difference test when the ratio of variance indicated a significant among-to-within group variation. Clinical chemistry data were analyzed by one-way analysis of variance (ANOVA) and Bartlett's test. If the F-test from ANOVA was significant, the Dunnett test was used to compare means from the control group and each of the test groups. If the results of the Bartlett's test was significant, the Kruskal-Wallis test was employed and the Mann-Whitney U test was used to compare means from the control group and each of the test groups. Mean absolute and relative organ weights were analyzed using the ANOVA. When the F-test for ANOVA was significant, paired comparisons between control and test groups were made with the Dunnett's test.

GLP: Yes

Test Substance: 93% 1,2-Diaminocyclohexane (DCH)
6% 2-Methylpentamethylenediamine (MPMD)
0.22% Hexamethylenediamine (HMD)
0.08% Water

Results: The DCH aerosol particle sizes (mass median aerodynamic diameter) ranged from 2.6 to 5.8 microns. Mean measured exposure concentrations were 10, 49, and 240 mg/m^3 for the 10, 50, and 250 mg/m^3 groups, respectively. Chamber oxygen concentrations measured either 20 or 21%. The mean % relative humidity in the exposure chambers was 43, 56, 42, and 52% for the 0, 10, 50, and 250 mg/m^3 groups, respectively. The mean temperature was 26, 25, 26, and 26ºC for the 0, 10, 50, and 250 mg/m^3 groups, respectively.

No clinical signs of toxicity, body weight or organ weight

changes, or compound-related changes in clinical laboratory analyses were seen at DCH concentrations of 10, 50, and 250 mg/m^3. Mean absolute and mean relative organ weights were similar to those of the controls immediately after the last exposure, and after the 14-day recovery period.

Microscopic examination showed dose-related inflammation and necrosis of the nasal mucosa in all DCH-exposed rats immediately after the 2-week exposure period. The nasal lesions were minimal in the 10 mg/m^3 group, mainly mild in the 50 mg/m^3 group, and moderate in the 250 mg/m^3 group. In addition, minimal to moderate inflammation and necrosis of the larynx/pharynx were observed in 2/5 rats in the 250 mg/m^3 group. This lesion of the larynx/pharynx was minimally present in 1/5 rats in the 50 mg/m^3 group and 1/5 rats in the 10 mg/m^3 group. Two out of 5 rats in the 250 mg/m^3 showed minimal to mild inflammation of the tracheal mucosa. After the 14-day recovery period, none of theses lesions were observed.

Reference: DuPont Co. (1993). Unpublished Data, Haskell Laboratory Report No. 555-93, "Two-Week Inhalation Toxicity Study with 1,2-Diaminocyclohexane in Rats" (December 1).

Kelly, D. P. et al. (1992). The Toxicologist, 12(1):357 (Abstract 1399) (RTECS/GU8749500).

Reliability: High because a scientifically defensible or guideline method was used.

Repeated Dose Study No. 2: Data for a mixture containing HMD, DCH, and MPMD

Type: **13-Week Repeated Dose Oral Toxicity**

Species/Strain: Rat/Crj: CD(SD)

Sex/Number: Male and female/15 per dose group

Exposure Period: 13 weeks

Frequency of Treatment: Daily

Exposure Levels: 0, 10, 30 and 125 mg/kg/day

Method: No specific test guideline was reported; however, a scientifically defensible approach was used to conduct the study.

Dose groups consisted of groups of 15 male and 15 female CD rats. The rats were housed individually in stainless steel cages in a temperature-, humidity-, and light- (12 hours light/12 hours dark) controlled room. Feed and water were available *ad libitum*.

Test article was prepared. Dosing route was oral gavage. The vehicle used was deionized water and the dosing volume was 10 mL/kg.

Mortality, morbidity and toxic signs were observed twice daily and recorded on the day noted. Detailed observations were conducted once weekly. Body weight and food consumption were measured weekly. Binocular ophthalmic examinations were conducted pretest and at week 13.

At week 13, 10 rats/sex/group were selected at random for clinical pathology (hematology, serum chemistry, and urinalysis). Rats were fasted 16 hours prior to sample collection. Hematological observations included hematocrit, hemoglobin, erythrocyte count, mean corpuscular hemoglobin, mean corpuscular volume, and mean corpuscular hemoglobin concentration (calculated), leukocyte count (total and differential), platelet count and reticulocyte count. Serum from the blood was used to determine levels of the following: aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, glucose, urea nitrogen, total bilirubin, total cholesterol, albumin, globulin (calculated), total protein, creatinine, sodium, potassium, chloride, calcium, inorganic phosphate, ornithine carbamoyltransferase, gammaglutamyl transpeptidase and creatine phosphokinase. Urine samples were collected from rats housed individually in stainless steel metabolism cages during the 16-hour fasting period. Urine was examined for determination of color, appearance, microscopic examination of sediment, specific gravity, volume, pH, protein, glucose, occult blood, nitrites, bilirubin, ketones, urobilinogen.

At study termination, macroscopic examinations were made on contents of the abdominal, thoracic and cranial cavities. All macroscopic abnormalities were recorded. Organ weights and ratios (organ:body and organ:brain) were determined for the following organs: adrenals, brain, heart, kidneys, liver, ovaries, testes. Microscopic pathological evaluation was conducted on the following tissues: adrenal (2), bone, bone marrow, bone marrow smear, brain (mid, fore and hind), eye (2), gastrointestinal tract (esophagus, stomach, duodenum, jejunum, ileum, cecum, colon, rectum), ovaries (2), testis with epididymus, heart, kidney, liver, lung, lymph nodes, mammary region (females), pancreas,

pituitary, prostate and seminal vesicle, salivary gland, sciatic nerve, skin, spinal cord, spleen thymic region, thyroid-parathyroid, trachea, urinary bladder, and uterus. The tissues were preserved in phosphate buffered saline, embedded in paraffin wax, and stained with hematoxylin and eosin. A full tissue complement was evaluated in the high dose group, control group, and all animals that died or were sacrificed *in extremis* during the study. Sections were prepared of all gross lesions and selected organs (liver, lungs, and kidneys) in the low and mid dose groups.

GLP: Yes

Test Substance: 1,6 diamino hexane 41.4% (HMD)
1,4-butane diamine 29.4%
Water 11.2%
2-methyl-1,5-diaminopentane 7.2% (MPMD)
1,2 diamino cyclohexane 6.8% (DCH)
1-Amino-2-methylamino cyclopentane 2.4%
Azacyclohexane 1.6%

Results: Two male rats died during the course of the study. One in the 125 mg/kg/day group at week 12 and one in the 30 mg/kg/day group following blood collection at week 13. Neither death was judged related to treatment (gavage error in the high dose group, sample collection error in the mid dose group).

Respiratory rales were observed in 4 of 15 males in the high dose groups. All other clinical signs were considered within normal limits.

No significant differences in body weight were observed between control and treated groups. A slight reduction in body weight gain was observed in female treated groups. No treatment related differences were observed in food consumption.

There were no treatment- related changes in hematological or serum biochemical analyses. A few hematological parameters were significantly different between the low dose and control groups (MCV and MCH); however, these values were within the range of historical controls and no dose-response was apparent. There were no treatment-related changes in urological analyses.

Organ weights and organ weight ratios in the treated groups were comparable to controls and no treatment-related changes were observed. No test article-related findings were

observed from macroscopic evaluations. No test article-related microscopic changes were observed during microscopic evaluations of tissues from animals in this study. All changes were considered to be incidental or spontaneous in nature and unrelated to treatment.

Histopathological evaluation of the gonads (testes and ovaries) and secondary sex organs (epididymus, prostate and seminal vesicle) was conducted. All observations were within normal limits with the exception of trace or mild inflammation of the prostate in 4 of 15 males in the high dose group, compared to 1 of 15 in the control group. Cystic follicles of the ovaries, considered mild, were observed in 1/14 controls and 1/14 high dose treated females; all other observations were within normal limits.

The no effect level in this study was 125 mg/kg/day.

Reference: Solutia Inc. (1984). Unpublished Data, Report No. IR-83-222, "Thirteen-Week Oral Toxicity Study in Rats" (March 11).

Reliability: High because a scientifically defensible or guideline method was used.

Repeated Dose Study No. 3: Data for a mixture containing HMD, DCH, and MPMD

Type:	**Four-Week Repeated Dose Oral Toxicity**
Species/Strain:	Rat/Sprague Dawley
Sex/Number:	Male and female/10 per dose group
Exposure Period:	28 days
Frequency of Treatment:	Daily
Exposure Levels:	0, 20, 50, 100, 250, and 500 mg/kg/day
Method:	No specific test guideline was reported; however, a scientifically defensible approach was used to conduct the study.

Dose groups consisted of groups of 10 male and 10 female CD rats. The rats were housed individually in stainless steel cages in a temperature-, humidity-, and light- (12 hours light/12 hours dark) controlled room. Feed and water were available *ad libitum*.

Test article was prepared. Dosing route was oral gavage. The vehicle used was deionized water and the dosing volume was 10 mL/kg.

	Mortality, morbidity and toxic signs were observed twice daily and recorded on the day noted. Detailed observations were conducted once weekly. Body weight and food consumption were measured weekly. At study termination, macroscopic examinations were made on contents of the abdominal, thoracic and cranial cavities. All macroscopic abnormalities were recorded. Organ weights and ratios (organ:body and organ:brain) were determined for the following organs: adrenals, brain, heart, kidneys, liver, ovaries, testes.
GLP:	Yes
Test Substance:	1,6-diaminohexane 41.4% (HMD) 1,4-butane diamine 29.4% Water 11% 2-methyl-1,5-diaminopentane 7.2% (MPMD) 1,2-diaminocyclohexane 6.8% (DCH) 1-amino-2-methylamino cyclopentane 2.4% 1-Azacyclohexane 1.6%
Results:	In the 500 mg/kg/day dose group, 6/10 males and 8/10 females died or were sacrificed *in extremis* during the study. Both males and females showed pronounced decreases in body weight gain and food consumption. Clinical signs observed during the dosing period included decreased activity, excessive salivation, labored breathing, rales and distention or firmness of the abdomen. Cause of premature death was not discernible from macroscopic findings. Changes in absolute and relative body weight were observed for several organs; however, these differences were likely related to decreased weight gain. In the 250 mg/kg dose group, 2/10 females died during the study. Similar clinical signs were observed at this dose levels, but they were observed in fewer animals. Body weight gain and food consumption were decreased in male animals, but not female animals. No changes in organ weights (absolute or relative) and no change in macroscopic findings were observed in this dose group. One death was recorded in both the 50 and 100 mg/kg/day group. These deaths were not attributed to treatment, but were consistent with dosing errors. No other differences between these groups and control animals were observed. No treatment related effects were observed in the 20 mg/kg/day group.

	The NOEL from this study was considered to be 100 mg/kg/day. The LOEL from this study was considered to be 250 mg/kg/day.
Reference:	Solutia Inc. (1984). Unpublished Data, Report No. IR-83-221, "Four-Week Oral Range-finding Study in Rats" (May 2).
Reliability:	High because a scientifically defensible or guideline method was used.

Additional References for Repeated Dose Toxicity: None Found.

5.3 Developmental Toxicity: No Data

5.4 Reproductive Toxicity

Reproductive Toxicity Study: Data for a mixture containing HMD, DCH, and MPMD

Species/Strain:	Rat/Crj: CD(SD)
Sex/Number:	Male and female/15 per dose group
Route of Administration:	Gavage
Exposure Period:	13 weeks
Frequency of Treatment:	Daily
Exposure Levels:	0, 10, 30, and 125 mg/kg/day
Method:	No specific test guideline was reported; however, a scientifically defensible approach was used to conduct the study.

A 13-week oral study was conducted in male and female rats (see section 5.2 for details on the study design). Terminal sacrifices occurred at week 13 (study termination). At study termination, macroscopic examinations were made on contents of the abdominal, thoracic and cranial cavities. All macroscopic abnormalities were recorded. Organ weights and ratios (organ:body and organ:brain) were determined for the following organs: adrenals, brain, heart, kidneys, liver, ovaries, testes. Microscopic pathological evaluation was conducted on the following tissues: adrenal (2), bone, bone marrow, bone marrow smear, brain (mid, fore and hind), eye (2), gastrointestinal tract (esophagus, stomach, duodenum, jejunum, ileum, cecum, colon, rectum), ovaries (2), testis with epididymus, heart, kidney, liver, lung, lymph nodes, mammary region (females), pancreas, pituitary, prostate and seminal vesicle. Salivary gland, sciatic nerve, skin, spinal cord, spleen thymic region, thyroid-parathyroid, trachea,

	urinary bladder and uterus. The tissues were preserved in phosphate buffered saline, embedded in paraffin wax, and stained with hematoxylin and eosin. A full tissue complement was evaluated in the high dose group, control group, and all animals that died or were sacrificed *in extremis* during the study. Sections were prepared of all gross lesions and selected organs (liver, lungs, and kidneys) in the low and mid dose groups.
GLP:	Yes
Test Substance:	1,6 Diamino hexane 41.4% (HMD) 1,4-Butane diamine 29.4% Water 11.2% 2-Methyl-1,5-diaminopentane 7.2% (MPMD) 1,2 Diamino cyclohexane 6.8% (DCH) 1-Amino-2-methylamino cyclopentane 2.4% Azacyclohexane 1.6%
Results:	Histopathological evaluation of the gonads (testes and ovaries) and secondary sex organs (epididymus, prostate, and seminal vesicle) was conducted. All observations were within normal limits with the exception of trace or mild inflammation of the prostate in 4 of 15 males in the high dose group, compared to 1 of 15 in the control group. Cystic follicles of the ovaries, considered mild, were observed in 1/14 controls and 1/14 high dose treated females; all other observations were within normal limits. Results on other organ systems are summarized in Section 5.2.
Reference:	Solutia Inc. (1984). Unpublished Data, Report No. IR-83-222, "Thirteen-Week Oral Toxicity Study in Rats" (March 11).
Reliability:	High because a scientifically defensible or guideline method was used.

Additional References for Reproductive Toxicity: None Found.

5.5 Genetic Toxicity

***In vitro* Genetic Toxicity Study No. 1: Data for a mixture containing DCH and HMD**

Type:	***In vitro* Bacterial Reverse Mutation Assay**
Tester Strain:	*Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98, and TA100
Exogenous Metabolic Activation:	With and without Aroclor 1254 induced rat liver S9 mix

Exposure Concentrations:	15, 50, 150, 500 and 1500 µg/plate
Method:	The procedure used in the test were based on the recommendations of the following guidelines: OECD Guideline 471 "Genetic Toxicology: *Salmonella typhimurium* Reverse Mutation Assay." Controls (positive and negative) and treated groups were evaluated in triplicate analyses. Positive controls were sodium azide, 9-aminoacridine, 2-nitrofluorene, and 2-anthramine. Negative control was solvent control of deionized water. Results were analyzed by linear regression per the method of Moore and Felton, 1983, Mutat. Res., 119:95.
GLP:	Yes
Test Substance:	Diaminocyclohexane 31.04% (DCH) Tetramethylene diamine 29.78% 2-Methyl-1,5-dimainoamino pentane 10.56% Hexamethylenediamine 6.37% (HMD) 1-Amino-2-methylamino cyclopentane 3.51% Hexamethylene imine 0.16%
Results:	Negative
Remarks:	No increase in mutation frequency in any of the tester strains was observed following treatment with the test substance under either activated or non-activated test conditions. Solvent and positive controls responded adequately.
Reference:	Solutia Inc. (1985). Unpublished Data, Report No. PK 850313, "Ames *Salmonella*/Microsome Plate Test (EPA/OECD), PH 301-MO-002-85 (PK-85-313) Amine Heads" (January 7)
Reliability:	High because a scientifically defensible or guideline method was used.

Additional References for *In vitro* Bacterial Reverse Mutation Assay:

Data from these additional sources support the study results summarized above, or provide insufficient data. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

Mitsubishi-Kaser (1991). Mitsubishi-Kaser Institute of Toxicological and Environmental Sciences, "Report of Results of Mutagenicity Test using Microorganisms" (June 14).

DuPont Co. (1989). Unpublished Data, Haskell Laboratory Report No. 817-88, "Mutagenicity Testing of 1,2-Cyclohexanediamine in the *Salmonella typhimurium* Plate Incorporation Assay" (February 15).

***In vitro* Genetic Toxicity Study No.2: Data for a mixture containing DCH and HMD**

Type:	***In vitro* Chromosome Aberration Test**
Cell Type:	CHO-K1-BH4
Exogenous Metabolic Activation:	With and without Aroclor 1254 induced rat liver S9 mix
Exposure Concentrations:	0, 100, 500, 1000, and 1500 µg/mL
Method:	The procedure used in the test were based on the recommendations of the following guidelines: EPA OTS 798.5375. Duplicate cultures were established for each control and treated group. The solvent control was distilled water. Positive controls were N-methyl-N-nitro-N-nitrosoguanidine and N-nitrosodimethyl amine. One hundred metaphases were scored for each data point (50 metaphases/culture from 2 parallel cultures). Chi square analysis was used to compare each data point with the concurrent solvent control. Significant differences in aberrations/cell were determined by one-tailed "t" tests comparing treated cultures to solvent controls.
GLP:	Yes
Test Substance:	Diaminocyclohexane 31.04% (DCH) Tetramethylene diamine 29.78% 2-Methyl-1,5-dimainoamino pentane 10.56% Hexamethylenediamine 6.37% (HMD) 1-Amino-2-methylamino cyclopentane 3.51% Hexamethylene imine 0.16%
Results:	Negative
Remarks:	100% cytotoxicity occurred in cultures at the 1500 µg/mL level without metabolic activation. The 3 remaining dose levels, 100, 500, and 1000 µg/mL were coded for analysis. No significant differences were observed between treated and control groups under nonactivated test conditions. The 500, 1000, and 500 µg/mL concentrations were scored for the S9 activated cultures. No significant differences were observed compared to solvent controls. Positive controls responded appropriately.
Reference:	Solutia Inc. (1985). Unpublished Data, Report No. PK 850314, "*In Vitro* Chromosome Aberration Analysis in Chinese Hamster Ovary (CHO) Cells, PH 320-MO-003-85 (PK-85-314) Amine Heads" (January 10).
Reliability:	High because a scientifically defensible or guideline method

was used.

Additional References for *In vitro* Clastogenicity: None Found.

Type: ***In vivo* Genetic Toxicity:** No Data

APPENDIX C

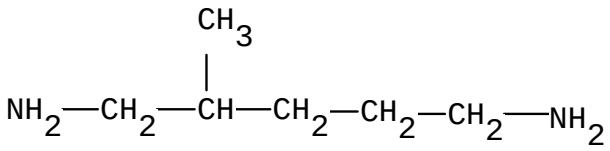
Existing published and unpublished data were collected and scientifically evaluated to determine the best possible study or studies to be summarized for each required endpoint. In the spirit of this voluntary program, other data of equal or lesser quality are not summarized, but are listed as related references at the end of each appropriate section, with a statement to reflect the reason why these studies were not summarized.

1.0 Substance Information

CAS Number: 15520-10-2

Chemical Name: 2-Methyl-1,5-pentanediamine

Structural Formula:



Other Names: 1,5-Diamino-2-methylpentane
2-Methyl-1,5-diaminopentane
2-Methyl-1,5-pentamethylenediamine
2-Methylpentamethylenediamine
2-Methylpentanediamine
Dytek® A Amine
Methylpentamethylenediamine
MPMD

Exposure Limits: 0.4 ppm (vapor); 2 mg/m^3 (particulate) (8- and 12-hour TWA): DuPont Acceptable Exposure Limit (AEL)

2.0 Physical/Chemical Properties

2.1 Melting Point

Value:	-50 to -60°C
Decomposition:	No Data
Sublimation:	No Data
Pressure:	No Data
Method:	No Data
GLP:	Unknown
Reference:	DuPont Co. (2001). Material Safety Data Sheet No. DU000185 (September 18).
Reliability:	Not assignable because limited study information was available.

Additional References for Melting Point: None Found.

2.2 Boiling Point

Value:	193°C
Decomposition:	No Data
Pressure:	760 mm Hg
Method:	No Data
GLP:	Unknown
Reference:	DuPont Co. (2001). Material Safety Data Sheet No. DU000185 (September 18).
Reliability:	Not assignable because limited study information was available.

Additional References for Boiling Point:

Estimated by MPBPWIN v1.40 as 179.40ºC (Adapted Stein and Brown Method) Calculated using MPBPWIN v1.40 as found in EPIWIN 3.05, Syracuse Research Company, Syracuse NY

2.3 Density

Value:	0.86 g/mL
Temperature:	25°C
Method:	No Data
GLP:	Unknown
Results:	No additional data.
Reference:	DuPont Co. (2001). Material Safety Data Sheet No. DU000185 (September 18).
Reliability:	Not assignable because limited study information was available.

Additional References for Density: None Found.

2.4 Vapor Pressure

Value:	0.22 mm Hg
Temperature:	20ºC
Decomposition:	No Data
Method:	No Data
GLP:	Unknown
Reference:	DuPont Co. (1985). Unpublished Data.
Reliability:	Not assignable because limited study information was available.

Value:	0.994 mm Hg
Temperature:	25^{o}C

Decomposition:	No Data
Method:	Modeled. Antoine & Grain method
GLP:	Not Applicable
Reference:	SRC MPBPWIN v1.40 in EPIWIN v3.05.
	Syracuse Research Corporation (MPBPWIN) program estimates the boiling point (at 760 mm Hg), melting point, and vapor pressure of organic compounds. The vapor pressure is estimated using the mean of the Antoine and Grain methods. A description of the methodology is detailed in:
	Antoine Method: Lyman, W. J. et al. (1990). Handbook of Chemical Property Estimation Methods, Chapter 14, American Chemical Society, Washington, DC.
	Modified Grain Method: Lyman, W. J. (1985). In: Environmental Exposure From Chemicals, Volume I, Chapter 2, Neely, W. B. and G. E. Blau (eds.), CRC Press, Inc., Boca Raton, FL.
Reliability:	Estimated value based on accepted model.

Additional Reference for Vapor Pressure:

DuPont Co. (2001). Material Safety Data Sheet No. DU000185 (September 18).

2.5 Partition Coefficient (log Kow)

Value:	0.27
Temperature:	25°C
Method:	Modeled. KOWWIN v. 1.66
GLP:	Not Applicable
Reference:	Meylan, W. M. and P. H. Howard (1995). J. Pharm. Sci., 84:83-92.
Reliability:	Estimated value based on accepted model.

Additional References for Partition Coefficient (log Kow): None Found.

2.6 Water Solubility

Value:	617,300 mg/L
Temperature:	25ºC
pH/pKa:	Estimated pKa: 10.2
Method:	Modeled.
	Solubility - WSKOWWIN v.1.40, module of EPIWIN v3.05

	(Syracuse Research Corporation). Water solubility is estimated from log Kow using molecular weight and molecular fragment correction factors.
	pKa – SPARC on-line calculator, University of Georgia.
GLP:	Not Applicable
Reference:	Solubility - Meylan, W. M. et al. (1996). Environ. Toxicol. Chem., 15:100-106. pKa - http://ibmlc2.chem.uga.edu/sparc/index.cfm.
Reliability:	Estimated value based on accepted models.

Additional References for Water Solubility:

DuPont Co. (2001). Material Safety Data Sheet No. DU000185 (September 18).

2.7 Flash Point

Value:	83°C; Autoignition @ 298°C
Method:	Closed cup
GLP:	Unknown
Reference:	DuPont Co. (2001). Material Safety Data Sheet No. DU000185 (September 18).
Reliability:	Not assignable because limited study information was available.

Additional References for Flash Point: None Found.

2.8 Flammability

Results:	Vapor will not form explosive mixture with air under normal conditions where good ventilation is present. It can form explosive mixture with air in a closed system when the vapor concentration is between the Lower Flammability Limit of 0.86 at 69ºC and the Higher Flammability Limit of 7.0 at 112ºC when the amount of oxygen is limited, but requires an ignition source.
Method:	No Data
GLP:	Unknown
Reference:	DuPont Co. (2001). Material Safety Data Sheet No. DU000185 (September 18).
Reliability:	Not assignable because limited study information was available.

Additional References for Flammability: None Found.

3.0 Environmental Fate

3.1 Photodegradation:

Concentration:	Not Applicable
Temperature:	Not Applicable
Direct Photolysis:	Not expected to be subject to photolysis because it lacks a chromophore structure that will adsorb wavelengths $\geq$ 290 nm
Indirect Photolysis:	AOP Program (v1.90) Results: ========== SMILES : NC(C)CCCCN CHEM : 2-methyl-1,5-pentanediamine MOL FOR: C6 H16 N2 MOL WT : 116.21 Hydrogen Abstraction = 37.2821x10^{-12} cm^3/molecule-sec Reaction with N, S and -OH = 42.0000x10^{-12} cm^3/molecule-sec Addition to Triple Bonds = 0.0000x10^{-12} cm^3/molecule-sec Addition to Olefinic Bonds = 0.0000x10^{-12} cm^3/molecule-sec Addition to Aromatic Rings = 0.0000x10^{-12} cm^3/molecule-sec Addition to Fused Rings = 0.0000x10^{-12} cm^3/molecule-sec Overall OH Rate Constant = 79.2821x10^{-12} cm^3/molecule-sec HALF-LIFE = 0.135 Days (12-hr day; 1.5x10^6 OH/cm^3) HALF-LIFE = 1.619 Hours
Breakdown Products:	Not Applicable
Method:	Inspection of chemical structure
GLP:	Not Applicable
Reference:	Harris, J. C. (1990). Rate of Aqueous Photolysis, Chapter 8 In Lyman,W. J. et al. (eds.). Handbook of Chemical Property Estimation Methods, American Chemical Society, Washington, DC.
Reliability:	Estimate based on known qualitative structure-activity relationships.

Additional References for Photodegradation: None Found.

3.2 Stability in Water:

Concentration:	Not Applicable
Half-life:	Greater than 1 year
% Hydrolyzed:	Not Applicable
Method:	The stability of this material in water is estimated based on established chemical principles. Amines are considered resistant to hydrolysis by Harris, J. C.

	in Lyman W. et al. (1990). Handbook of Chemical Property Estimation Methods, page 7-6, American Chemical Society, Washington, DC. This indicates a hydrolytic half-life of greater than one year.
GLP:	Not Applicable
Reference:	Lyman W. et al. (1990). Handbook of Chemical Property Estimation Methods, page 7-6, American Chemical Society, Washington DC.
Reliability:	Estimate based on chemical principles.

Additional References for Stability in Water: None Found.

3.3 Transport (Fugacity):

Media:	Air, Water, Soil, and Sediments	
Distributions:	Air:	0.0874%
	Water:	46.1%
	Soil:	53.7%
	Sediments:	0.078%
Half-life:	Air:	3.24h
	Water:	360 h
	Soil:	360 h
	Sediments:	1440 h
Adsorption Coefficient:	Log Koc = 0.763	
Desorption:	Not Applicable	
Volatility:	Henry's Law Constant = 8.48e-010 atm-m^3/mole	
Method:	Calculated according to Mackay, Level III, Syracuse Research Corporation EPIWIN v3.05. Emissions (1000 kg/hr) to air, water, and soil compartments using standard EPA model defaults.	
	Data Used: Molecular Weight: 116.21 Henry's Law Constant: 3.21e-9 atm-m^3/mole (HENRYWIN Program) Vapor Pressure: 0.994 mm Hg Log Kow: 0.27 Soil Koc: 0.763	
GLP:	Not Applicable	
Reference:	Syracuse Research Corporation EPIWIN v3.05 contains a Level III fugacity model. The methodology and programming approach were developed by Dr. Donald MacKay and coworkers and are detailed in:	
	Mackay, D. (1991). Multimedia Environmental Models:	

The Fugacity Approach, pp. 67-183, Lewis Publishers, CRC Press.

Mackay, D. et al. (1996). Environ. Toxicol. Chem., 15(9):1618-1626.

Mackay, D. et al. (1996). Environ. Toxicol. Chem., 15(9):1627-1637.

Reliability: Estimated value based on an accepted model.

Additional References for Transport (Fugacity): None Found.

3.4 Biodegradation

Value: The theoretical oxygen demand (ThOD) was calculated as 4.032 mg O_2/mg test substance.

For the test substance, the following biodegradability was found:
0% after 7 days,
1% after 14 days,
46% after 17 days,
102% after 21 days and 28 days.

Additional nitrate measurements in the 28-day samples confirmed a total nitrification of the test substance during the test period. Therefore, the test substance was classified as ready biodegradable according to the Guidelines. Moreover, it was found that an inhibiting effect on the biochemical degradation of the reference substance at the concentration tested could not be excluded.

Breakdown Products: No Data

Method: The procedure used in the test were based on the recommendations of the following guideline: OECD Guideline No. 301 D (which corresponds to the EC-Method, Part C.4, Part E): "Ready Biodegradability: Closed Bottle Test."

The biochemical degradability of the test substance at 293ºK (20ºC) was determined. The mineral nutrient solution was prepared according to the prescriptions of the Guideline; the inoculum was a composite made from equal parts of the total effluent and the reflux of an activated sludge plant. The oxygen depletion was measured after 7, 14, 17, 21, and 28 days by means of an oxygen electrode. Control- and

	blank-series without test substance were run simultaneously and the effectiveness of the inoculum was confirmed (in a 3rd series with sodium acetate as the reference substance) and found to be 102% after 28 days under the conditions of the test.
GLP:	Yes
Reference:	DuPont Co. (1997). Unpublished Data, NATEC Institut Study No. 969410/2.2, "Biochemical Degradability, Test Substance: MPMD" (June 4).
Reliability:	High because a scientifically defensible or guideline method was used.

Additional References for Biodegradation: None Found.

3.5 Bioconcentration:

Value:	BCF = 3.16
Method:	Modeled. BCFWIN v. 2.4 module of EPINWIN v3.05 (Syracuse Research Corporation). BCFWIN estimates the bioconcentration factor (BCF) of an organic compound using the compound's log octanol-water partition coefficient (Kow) with correction factors based on molecular fragments.
GLP:	Not Applicable
Reference:	"Improved Method for Estimating Bioconcentration Factor (BCF) from Octanol-Water Partition Coefficient", SRC TR-97-006 (2nd Update), July 22, 1997; prepared for: Robert S. Boethling, EPA-OPPT, Washington, DC; Contract No. 68-D5-0012; prepared by: William M. Meylan, Philip H. Howard, Dallas Aronson, Heather Printup and Sybil Gouchie; Syracuse Research Corp.
Reliability:	Estimated value based on an accepted model.

Additional References for Bioconcentration: None Found.

4.0 Ecotoxicity

4.1 Acute Toxicity to Fish

Type:	**48-hour LC_{50}**
Species:	Orfe, *Leuciscus idus melanotus*
Value:	130 mg/L
Method:	The procedure used in the test were based on the recommendations of the following guideline: German Standard "Deutsches Einheitsverfahren" DIN 38 412, Part 15.

The effects of the test substance on *Leuciscus idus melanotus* within 48 hours were examined and compared to a negative control. Ten fish were exposed to various concentrations of the test substance (0, 100, 180, 320, and 580 mg/L) in water without using any solubilising agent. The test was performed using a static test procedure. Two hours before test start 15 L of each concentration were prepared and distributed in the test containers. These solutions were stored under test conditions until the test started. After this precoating time, the solutions were replaced by freshly prepared solutions and 10 fish were introduced into the test containers (1 test container for each concentration).

The main test criteria were the mortalities after 24 and 48 hours in each solution. Those animals showing no reaction within a few seconds after touching the caudal peduncle were considered to be dead. Dead animals were removed at the observation times and test containers were exchanged and cleaned. Other significant effects compared to the control observed in the test containers were also documented.

Ambient air was pumped by means of an aquarium aerator through silicon rubber tubes and "flow-out stones" into the aquaria. The air flow was adjusted in order to maintain an oxygen concentration of >80% of the saturation. No feeding occurred during the test. Sixteen hours of light and 8 hours of darkness were provided during the test. Water hardness was 2.2 mole $CaCO_3$/L. Oxygen content, pH, and temperature were recorded at 0.1, 24, and 48 hours.

GLP: Yes

Test Substance: 2-Methyl-1,5-pentanediamine, purity 99%

Results: After evaluation of the results with a "Probit" method, the following toxicity data were obtained:

NOEC = 100 mg/L (nominal);
0% mortality at 100 mg/L (nominal);
LC_{50} = 130 mg/L (nominal);
100% mortality = 180 mg/L (nominal).

No other effects of the test substance in the test containers compared to the control were observed.

The pH was 8.4 when measured at 0.1, 24, and 48 hours. The oxygen content (% of saturation) was 92, 93, and 92 at 0.1, 24, and 48 hours, respectively. The water temperature

	was 20.1, 20.2, and 20.2ºC at 0.1, 24, and 48 hours, respectively.
Reference:	DuPont Co. (1997). Unpublished Data, NATEC Institut Study No. 969410/2.3, "Acute Toxicity Test on the Orfe (*Leuciscus idus melanotus*) Static Test Procedure, 48 Hours" (June 3).
Reliability:	Medium because a suboptimal study design (nominal concentrations and 48 hours) was used for testing.

Type:	**96-hour LC_{50}**
Species:	Freshwater fish
Value:	409.7 mg/L
Method:	Modeled, ECOSAR (using log Kow of 0.27)
GLP:	Not Applicable
Test Substance:	2-Methyl-1,5-pentanediamine
Results:	No additional data.
Reference:	Meylan, W. M. and P. H. Howard (1999). User's Guide for the ECOSAR Class Program, Version 0.993 (Mar 99), prepared for J. Vincent Nabholz and Gordon Cas, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics, Washington, DC, prepared by Syracuse Research Corp., Environmental Science Center, Syracuse, NY 13210 (submitted for publication).
Reliability:	Estimated value based on accepted model.

Additional References for Acute Toxicity to Fish: None Found.

4.2 Acute Toxicity to Invertebrates:

Type:	**48-hour EC_{50}**
Species:	Daphnid
Value:	24.2 mg/L
Method:	Modeled, ECOSAR (using $\log_{10}$ Kow of 0.27)
GLP:	Not Applicable
Test Substance:	2-Methyl-1,5-pentanediamine
Results:	No additional data.
Reference:	Meylan, W. M. and P. H. Howard (1999). User's Guide for the ECOSAR Class Program, Version 0.993 (Mar 99), prepared for J. Vincent Nabholz and Gordon Cas, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics, Washington, DC, prepared by Syracuse Research Corp., Environmental Science Center, Syracuse, NY 13210 (submitted for publication).
Reliability:	Estimated value based on accepted model.

Additional References for Acute Toxicity to Invertebrates: None Found.

4.3 Acute Toxicity to Aquatic Plants:

Type:	**96-hour EC_{50}**
Species:	Green algae
Value:	25.1 mg/L
Method:	Modeled, ECOSAR (using $\log_{10}$ Kow of 0.27)
GLP:	Not Applicable
Test Substance:	2-Methyl-1,5-pentanediamine
Results:	No additional data.
Reference:	Meylan, W. M. and P. H. Howard (1999). User's Guide for the ECOSAR Class Program, Version 0.993 (Mar 99), prepared for J. Vincent Nabholz and Gordon Cas, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics, Washington, DC, prepared by Syracuse Research Corp., Environmental Science Center, Syracuse, NY 13210 (submitted for publication).
Reliability:	Estimated value based on accepted model.

Additional References for Acute Toxicity to Aquatic Plants: None Found.

5.0 Mammalian Toxicity

5.1 Acute Toxicity

Type:	**Oral LD_{50}**
Species/Strain:	Male rats/Crl:CD®
Value:	1690 mg/kg (95% confidence limits, 1490-1930 mg/kg)
Method:	No specific test guideline was reported; however, a scientifically defensible approach was used to conduct the study. Ten male rats/group were administered single oral doses of the test material via intragastric intubation at dose levels of 1000, 1300, 1700, 2000, or 3000 mg/kg. The test material was suspended in distilled water. The rats were 8 weeks old when dosed. Survivors were weighed and observed daily until signs of toxicity subsided and then at least every other day (weekends excluded) throughout a 14-day recovery period. No pathologic examinations were conducted. The LD_{50} value was calculated from mortality data using the method of D. J. Finney.
GLP:	Yes
Test Substance:	2-Methyl-1,5-pentanediamine, purity >90%
Results:	Mortality ratios of 0/10, 2/10, 4/10, 8/10, and 10/10 were reported for the 1000, 1300, 1700, 2000, and 3000 mg/kg

groups, respectively.

Rats administered 1000 mg/kg exhibited slight to severe weight loss for 1-2 days after dosing. Other clinical signs included salivation (test day 1), lung noise (test days 1-2), diarrhea (test days 2-3), and stained perineum (test day 2). At lethal doses, rats exhibited slight to severe weight loss for 1-8 days after dosing followed by recovery. Shortly after dosing, blood was observed in the urine of rats dosed at 1700 mg/kg and above. This was not seen 24 hours after dosing. Predominant clinical signs included diarrhea (test days 2-8); discharge from the eyes (test days 2-8), nose (test days 1-8), and mouth (test days 1-7); lung noise (test days 1-7); and hunched posture (test days 2-8).

The presence of blood in the urine was confirmed in an additional experiment where 4 rats were dosed (2 at 1000 mg/kg and 2 at 3000 mg/kg) and placed in metabolism racks. Urine samples collected over a 2-hour post-dosing period were tested with Ames Multistix reagent strips for occult blood. Three of 4 urine samples were positive for blood. Blood was taken from 1 rat per dose level after dosing and approximately 2 hours post-dosing. Hematology measurements (hematocrit, red blood cell count, and microscopic exam of whole blood) indicated normal values.

Reference: DuPont Co. (1984). Unpublished Data, Haskell Laboratory Report No. 218-84, "Median Lethal Dose (LD_{50}) in Rats" (May 11).

Reliability: High because a scientifically defensible or guideline method was used.

Additional Reference for Acute Oral Toxicity:

Data from this additional source were not summarized because the focus of the study was a Class B Poison Test.

DuPont Co. (1979). Unpublished Data, Haskell Laboratory Report No. 135-79, "Class B Poison Test – Oral Toxicity" (March 23).

Type: **Inhalation LC_{50}**

Species/Strain: Male and female rats/Crl:CD®BR

Exposure Time: 1 hour

Value: Male rats: 2.9 mg/L (no confidence limits)
Female rats: 4.1 mg/L (95% confidence limits, 1.8–11 mg/L)

Method: No specific test guideline was reported; however, a scientifically defensible approach was used to conduct the

study.

Five male and five female rats/group were exposed to 0.37, 1.7, 2.5, 6.6, or 10 mg/L of the test substance. The rats were 8-10 weeks old and weighed 231-288 g (male rats) or 196-244 g (female rats) at study initiation. Each group was exposed nose-only to an aerosol/vapor atmosphere of the test substance in air in a 38-L glass exposure chamber. Rats were observed for clinical signs of toxicity during exposure if possible, and upon release from the restrainers after exposure. During the 14-day recovery period, surviving rats were weighed and observed daily for the first 7 days after exposure and daily except on weekends during the second 7 days after exposure. No pathologic examinations were conducted.

Atmospheres of the test substance were generated by pumping the liquid test material into an Instatherm® Flask heated to 187-228°C. The liquid was metered with an infusion pump. Nitrogen introduced at the flask swept the vapors into a glass transfer tube. Dilution air was added in the transfer tube where an aerosol/vapor mixture was formed. The vapor/aerosol mixture then discharged directly into a 38-L cylindrical glass exposure chamber and was dispersed with a baffle to promote uniform chamber distribution. In order to attain a higher chamber concentration in the last exposure, 2 syringes and 2 Instatherm® flasks were used to increase the vaporization capacity. Chamber concentrations were controlled by varying the test material feed rates into the flask.

The atmospheric concentration of the test substance was monitored at approximately 15-minute intervals during each exposure. Samples were analyzed via gas chromatography. Aerodynamic particle size was determined with a cascade impacter during each exposure. Chamber temperature was measured with a mercury thermometer, oxygen concentration was measured with an oxygen monitor, and relative humidity was measured with a psychometer.

The LC_{50} was calculated by the method of Finney, 1971.

GLP: Yes

Test Substance: 2-Methyl-1,5-pentanediamine, purity 99.5%

Results: The mass median aerodynamic diameter (MMD) for the 0.37, 1.7, 2.5, 6.6, and 10 mg/L groups was 3.4, 4.2, 3.8, 3.8, and 3.1 μm, respectively.

Mortality ratios of 1/5, 3/5, 1/5, 2/5, and 5/5 were reported for male rats at 0.37, 1.7, 2.5, 6.6, and 10 mg/L, respectively. Mortality ratios of 0/5, 1/5, 2/5, 2/5, and 5/5 were reported for female rats at 0.37, 1.7, 2.5, 6.6, and 10 mg/L, respectively.

Two male rats and one female rat in the 10 mg/L exposure group died during exposure. All other rats in this group died within 48 hours of exposure. Deaths occurred at lower exposure concentrations at various times during the14-day recovery period. There was no clear dose-related trend seen with respect to when the deaths occurred.

During exposure, rats in the 1.7 and 2.5 mg/L exposure groups showed red nasal discharge. In addition, rats in the 2.5 mg/L group showed a decreased response to sound. Rats in the 6.6 and 10 mg/L groups could not be seen during exposure, therefore, it was not possible to note clinical signs during exposure. Immediately after being released from their restrainers, rats in the 0.37 and 1.7 mg/L groups showed red nasal and ocular discharges. Upon release from their restrainers, rats exposed to 2.5 mg/L and higher showed red ocular, nasal, or oral discharges, labored breathing, and gasping. In addition, rats in the 10 mg/L group showed hunched posture.

During the 14-day recovery period, the only clinical sign of toxicity observed in the rats exposed to 0.37 mg/L was slight to severe weight loss, which occurred over 1 to 3 days. Numerous clinical signs of toxicity were observed in both male and female rats exposed to 1.7 mg/L and higher, but there were no clear dose-response trend seen among these exposure groups. Common clinical signs observed in rats exposed to higher concentrations included slight to severe weight loss, red-ocular, -nasal, or –oral discharge, wet urine- or feces-stained perineum, diarrhea, high carriage, hunched posture, lung noise, labored breathing, and gasping.

Reference:

DuPont Co. (1988). Unpublished Data, Haskell Laboratory Report No. 265-88, "Inhalation One-Hour Median Lethal Concentration (LC_{50}) of Dytek®A Amine in Rats by IMDG Protocol" (August 21) (also cited in RTECS/SA0248500 and TSCA Fiche OTS0556331).

Kelly, D. P. et al. (1992). The Toxicologist, 12(1):357 (Abstract 1399).

Reliability:	High because a scientifically defensible or guideline method was used.

Additional References for Acute Inhalation Toxicity: None Found.

Type: **Acute Dermal Toxicity:** No Data.

Type:	**Dermal Irritation**
Species/Strain:	Male and female rabbits/New Zealand White
Method:	No specific test guideline was reported; however, a scientifically defensible approach was used to conduct the study. On the day prior to study initiation, the hair of 6 rabbits was closely clipped to expose the back from the scapular to the lumbar region. The rabbits weighed from 2985 to 3567 grams on the day of treatment. Each rabbit was placed in a stock. A 0.5 mL aliquot of the test material was applied directly on the test site beneath a gauze square that was held in place with tape. Three minutes after application of the test material, the test sites were gently washed with warm water to remove excess test material and the skin was gently patted dry. After evaluation of the test sites for skin irritation, the rabbits were returned to their cages. Approximately 24 and 48 hours after application of the test material, the test sites were again evaluated for necrosis, erythema, edema, and other evidence of dermal effects. Each test site was scored according to the Draize scale. The adjacent areas of untreated skin were used for comparison.
GLP:	No
Test Substance:	2-Methyl-1,5-pentanediamine, purity 98.5%
Results:	The test substance produced severe erythema with necrosis in all rabbits at the end of the treatment period (approximately 3 minutes after application). Severe erythema with necrosis persisted in all rabbits at the 24- and 48-hour evaluation time point. Blanching was also observed at 48 hours post-treatment. Moderate edema was observed in all rabbits at 24 and 48 hours post-treatment. Under the conditions of the study, the test substance was a skin corrosive agent when applied to the clipped intact skin of rabbits.
Reference:	DuPont Co. (1986). Unpublished Data, Haskell Laboratory Report No. 620-86, "Skin Corrosion Test of 2-Methylpentamethylenediamine in Rabbits for International Maritime Organization Packaging Classification"

(November 14) (also cited in TSCA Fiche OTS0555312).

Reliability: High because a scientifically defensible or guideline method was used.

Additional References for Dermal Irritation:

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

DuPont Co. (1979). Unpublished Data, Haskell Laboratory Report No. 139-79, "Department of Transportation Skin Corrosion Test on Rabbit Skin" (March 30).

DuPont Co. (1985). Unpublished Data, Haskell Laboratory Report No. 504-84, "Department of Transportation Skin Corrosion Test on Rabbits" (January 22).

DuPont Co. (1988). Unpublished Data, Haskell Laboratory Report No. 177-88, "Dermal Sensitization Study with Dytek® A Amine in Guinea Pigs" (April 4).

DuPont Co. (1984). Unpublished Data, Haskell Laboratory Report No. 282-84, "Skin Sensitization Test on Guinea Pigs" (June 4).

Type: **Dermal Sensitization**

Species/Strain: Guinea pigs/Duncan Hartley albino

Method: No specific test guideline was reported; however, a scientifically defensible approach was used to conduct the study.

A rangefinding study was conducted on 3 female guinea pigs. Aliquots (approximately 0.05 mL) of 50%, 10%, 5%, and 1% (v/v) emulsions of the test material in distilled water were applied and lightly rubbed onto separate test sites on the shaved, intact skin of each guinea pig's back. Irritation responses were scored approximately 24 and 48 hours after treatment.

The primary irritation phase was conducted in 10 guinea pigs (5 male and 5 female), weighing from 475 to 659 grams, by applying and lightly rubbing in 1 drop (approximately 0.05 mL) of 5% and 0.5% (v/v) emulsions of the test material in distilled water onto separate sites of shaved, intact skin of each guinea pig. Ten vehicle control guinea pigs (5 male and 5 female), weighing from 512 to 626 grams, were also treated by applying and lightly rubbing in 1 drop (approximately 0.05 mL) of distilled water onto separate sites of shaved, intact skin of each guinea pig. In

addition 10 positive control guinea pigs (5 male and 5 female), weighing between 496 and 617 grams, were treated by applying and lightly rubbing in 1 drop of 30% and 3% (w/v) suspensions of p-phenylenediamine in acetone:dimethyl phthalate (1:9 v/v) onto separate sites of shaved, intact shoulder skin of each guinea pig. Dermal responses were scored approximately 24 and 48 hours after application of the test material.

Two days after the primary dermal application phase, the induction phase of the study was initiated using the same test guinea pigs. Induction consisted of a series of 4 sacral intradermal injections (1 each week) of 0.1 mL of a 1.0% (v/v) emulsion of Dytek A in saline. The same injection procedure was followed for the 10 vehicle control guinea pigs using physiologic saline and for the 10 positive control guinea pigs using 0.1 mL of a 1.0% (w/v) suspension of p-phenylenediamine in acetone:dimethyl phthalate (1:9 v/v). Skin responses were evaluated approximately 24 hours after each injection.

Two weeks after the last induction treatment, the test guinea pigs were challenged for sensitization by applying and lightly rubbing in 1 drop of 5% and 0.5% (v/v) emulsions of the test material in distilled water onto separate sites of shaved, intact skin. The 10 vehicle control guinea pigs received identical topical applications of the test substance. The positive control animals guinea pigs were challenged for sensitization by applying and lightly rubbing in 1 drop of 30% and 3% (w/v) suspensions of p-phenylendiamine in acetone:dimethyl phthalate (1:9) onto separate sites of shaved, intact skin. Responses were scored approximately 24 and 48 hours after application of the test material.

GLP: Yes

Test Substance: 2-Methyl-1,5-pentanediamine, purity 99.5%

Results: In the rangefinding test, the test substance produced strong erythema to necrosis in the 50% and 10% test sites. No dermal irritation was observed in the 5% or 1% concentration sites.

During the primary irritation phase, no dermal irritation was observed in the test, vehicle, or control guinea pigs. Mild erythema was observed in 5 test guinea pigs in the 5% concentration site during the challenge phase. Mild erythema was observed in 1 vehicle control guinea pig in the 5% site. No dermal irritation was observed in the

	0.5% concentration sites of the test or vehicle control guinea pigs. Mild erythema to necrosis was observed in the positive control guinea pigs at 24 and 48 hours in the 30% concentration sites. No to moderate erythema was observed in the 3% concentration site. Under the conditions of the study, the test substance did not produce delayed hypersensitivity or allergic reactions.
Reference:	DuPont Co. (1988). Unpublished Data, Haskell Laboratory Report No. 177-88, "Dermal Sensitization Study with Dytek® A Amine in Guinea Pigs" (April 4).
Reliability:	High because a scientifically defensible or guideline method was used.

Additional Reference for Dermal Sensitization:

Data from this additional source support the study results summarized above. This study was not chosen for detailed summarization because the data were not substantially additive to the database.

DuPont Co. (1984). Unpublished Data, Haskell Laboratory Report No. 282-84, "Skin Sensitization Test on Guinea Pigs" (June 4).

Type:	**Eye Irritation**
Species/Strain:	Rabbits/Albino
Method:	No specific test guideline was reported; however, a scientifically defensible approach was used to conduct the study. One-tenth mL of the undiluted test material was placed into the right conjunctival sac of each of 3 albino rabbits. After 20 seconds, 1 treated eye was washed with tap water for 1 minute and another was washed with tap water for 15 minutes. The treated eye of the 3rd rabbit was not washed. Observations of the cornea, iris, and conjunctiva were made with a hand-slit lamp at 1 and 4 hours, and at 1, 2, 3, 7, and 11 days. Fluor-I-strip® stain, Hemestix® (when needed), and a biomicroscope were used at examinations after the day of treatment.
GLP:	No
Test Substance:	2-Methyl-1,5-pentanediamine, purity 99.2%
Results:	The test substance caused immediate, complete corneal opalescence and necrosis of the conjunctiva and outer lid in the unwashed rabbit eye. Effects on the iris were not seen due to the severity of the corneal irritation; however, at 1-3 days the eye did not react to light. The rabbit was

sacrificed at 3 days because of the obvious corrosive nature of the test material.

In the eye washed for 1 minute, the test substance caused severe corneal irritation with a large ulcer, moderate iritis, clouds of precipitate in the anterior chamber, and necrosis of the conjunctiva and outer lids. At 10 days, the eye appeared shriveled and at 11 days the animal was sacrificed.

Water washing for 15 minutes did not lessen the ocular effects. This eye was similar to the one washed for 1 minute.

Reference: DuPont Co. (1979). Unpublished Data, Haskell Laboratory Report No. 99-79, "Eye Irritation Test in Rabbits" (March 30).

Reliability: High because a scientifically defensible or guideline method was used.

Additional References for Eye Irritation: None Found.

5.2 Repeated Dose Toxicity

Type:	**28-Day Repeated Dose Oral Toxicity**
Species/Strain:	Rats/Crl:CD®BR
Sex/Number:	Male and female 10/sex for 0 and 10,000 ppm groups 5/sex for 300 and 3000 ppm groups
Exposure Period:	28 days
Frequency of Treatment:	Daily
Exposure Levels:	0, 300, 3000, and 10,000 ppm
Method:	The procedure used in the test were based on the recommendations of the following guideline: OECD Guideline Section 407.

Groups of rats were fed diets containing 0, 300, 3000, or 10,000 ppm for 28 days. Rats were 51 days of age at study start. All rats were individually housed in stainless steel, wire mesh cages. Male and female rats were housed on separate cage racks. Animal rooms were targeted at a temperature of 23±2ºC and a relative humidity of 50±10%. Throughout the study, all rats were fed the diet of their respective treatment group and provided water *ad libitum*. Animal rooms were maintained on a timer-controlled, 12 hour light/12-hour dark cycle. Excursions outside these ranges were of small magnitude and/or brief duration and did

not adversely affect the validity of the study.

The test substance was added to rodent chow and thoroughly mixed in a high-speed mixer. Control diets were also mixed for the same period of time. All diets were prepared weekly and refrigerated until used. Samples were collected from the diet preparations and analyzed for concentration verification, homogeneity of the test compound in the diet, and stability of the test compound in the diet.

All rats were weighed at least twice weekly throughout the dosing and recovery periods. At each weighing, each rat was individually handled and examined for abnormal behavior and appearance. An additional cage-site examination to detect moribund or dead rats was done daily. The amount of food consumed weekly by each test group was determined throughout the study. From these determinations, group mean daily food consumption per rat was calculated.

Clinical laboratory evaluations were performed on all rats selected for the study at the end of the treatment period, test day 28, and on all the surviving rats at the end of the recovery period, test day 42. Two days prior to collection of blood samples for clinical evaluation, rats were placed in metabolism cages for acclimatization. The day before blood collection, these rats were fasted for approximately 16 hours. Urine was collected from each rat during this period and 13 urine chemistry parameters were measured or calculated. At the conclusion of this period, blood samples for hematological and clinical chemistry measurements were collected. Nine hematology parameters and 18 blood chemistry parameters were measured or calculated. .

After approximately 28 days of continuous feeding, 5 rats/sex from the control and high-dose groups and all the rats from the low and intermediate groups were sacrificed and necropsied. The surviving rats from the control and high dose groups were sacrificed at the end of the 14-day recovery period. The liver, kidneys, adrenals, and testes were weighed at necropsy. Approximately 35 tissues (including reproductive organs: prostate, testes, epididymides, seminal vesicles, mammary gland, ovaries, uterus, and vagina) were removed and prepared for histological examination. The tissues from the high and control groups and from rats killed in extremis were

histologically examined.

Body weights, body weight gains, organ weights, and clinical laboratory measurements were analyzed by a one-way analysis of variance. When the test for differences among test group means (F test) was significant, pairwise comparisons between test and control groups were made with Dunnett's test. Bartlett's test for homogeneity of variances was performed on the organ weight and clinical laboratory data and, if significant, was followed by nonparametric procedures.

GLP: Yes

Test Substance: 2-Methyl-1,5-pentanediamine, purity 99.3%

Results: The estimated mean daily intake of the test substance in male rats in the 300, 3000, and 10,000 ppm was 24.3, 238.5, and 745.2 mg/kg body weight/day, respectively. In female rats, these values were 27.5, 275.7, and 791.0 mg/kg body weight/day, respectively. Analysis of diet samples revealed that the test material was slightly unstable at room temperature at concentrations of 300 ppm and higher. Analysis of these samples revealed concentrations that were 65-80% of the target concentrations.

Body weight of male rats (all doses) and female rats (300 and 3000 ppm) and body weight gain of male rats (all doses) were not adversely affected by test substance administration. Mean body weights of female rats in the 10,000 ppm group were non-significantly depressed during the exposure and recovery periods. Mean body weight gains of female rats in the 10,000 ppm group were significantly depressed during the exposure period, but were similar to controls during the recovery period.

Dietary concentrations of 300, 3000, or 10,000 ppm in male rats and 300 or 3000 ppm in female rats had no effect on food consumption over the 0-29 day test period. Food consumption for female rats from the 10,000 ppm group was lower (approximately 13%) compared to control rats over the course of the study. Overall mean food efficiency values of male and female rats were similar to those of rats in the control groups.

No adverse clinical signs of toxicity were observed during the study. One male rat from the 10,000 mg/kg group was killed *in extremis* on test day 5 and submitted for pathological examination. Pathological evaluation revealed

	that this rat was anorectic and had diarrhea. Microscopically, there were a few small ulcers in the non-glandular portion of the stomach. There was also evidence of atrophy of the thymus and hypospermia in the epididymides. The cause of the deterioration of this animal could not be determined. Since this death was an isolated event, it is unlikely to be related to the test material. The hematologic, clinical chemical, and urinalysis parameters were not affected by test substance administration. There were no significant differences in organ weight data, and pathological examination revealed no compound-related changes. There was a significant increase in testicular weight of the high-dose group sacrificed at the end of the recovery period compared to controls. However, this finding was considered to biologically insignificant since gross or microscopic lesions were not observed. The NOEL was 10,000 ppm for male rats and 3000 ppm for female rats.
Reference:	DuPont Co. (1990). Unpublished Data, Haskell Laboratory Report No. 366-90, "Repeated Dose Oral Toxicity: 28-Day Study with Dytek® A Amine Feeding Study in Rats" (December 6).
Reliability:	High because a scientifically defensible or guideline method was used.
Type:	**2-Week Inhalation Toxicity Study**
Species/Strain:	Rats/Crl:CD®BR
Sex/Number:	Male/10 per group
Exposure Period:	2 weeks
Frequency of Treatment:	6 hours/day, 5 days/week
Exposure Levels:	0, 10, 50, 250 mg/m^3
Method:	No specific test guideline was reported; however, a scientifically defensible approach was used to conduct the study. Groups of rats were exposed via nose-only inhalation to aerosol/vapor mixtures of the test substance at design concentrations of 0, 10, 50, or 250 mg/m^3. Rats were exposed 6 hours/day, 5 days/week for 2 weeks, and were retained for a 14-day post-exposure recovery period.

Rats were approximately 7 weeks old and weighed 207-243 g at study initiation. Environmental conditions of animal rooms were targeted at a temperature of 23±2°C and relative humidity of 50±10%. However, during most of the study, the animal room and chamber humidity readings were below 40% due to cold weather conditions combined with poor humidity control in the laboratory. This did not appear to affect the integrity of the study.

Aerosol and vapor atmospheres of the test substance were generated by pumping the test material to a heated Instatherm® flask. Nitrogen introduced at the flask swept the aerosol/vapor mixture into the chambers. Dilution air was added to the stream just prior to the entry port of the chamber.

The atmospheric concentration of the test substance was monitored at approximately hourly intervals during each exposure. Samples were analyzed via gas chromatography. Aerodynamic particle size was determined weekly with a cascade impacter. Chamber temperature, oxygen concentration, and relative humidity were measured.

All rats were monitored for body weight and clinical signs of toxicity throughout the study. At the end of the exposure period, blood and urine samples were collected from all rats for clinical analyses, and 5 rats per group were sacrificed for pathologic evaluation. After a 14-day recovery period, the remaining rats were given the same clinical and pathological examinations. Urine samples were collected overnight from all surviving rats after the 9th exposure, and from the surviving 5 rats per group (4 rats in the 250 mg/m^3 group) on the 13th day of recovery. Thirteen urine chemistry parameters were measured or calculated. Blood samples were taken from all surviving rats after the 10th exposure, and from the remaining 5 rats per group (4 rats in the 250 mg/m^3 group) on the 14th day of recovery. Eight hematology parameters and 19 blood chemistry parameters were measured or calculated.

The first 5 rats per group (4 in the 250 mg/m^3 group) were sacrificed after the 10th exposure and the remaining rats were sacrificed on the 14th day of recovery for gross and histopathological evaluations. The liver, brain, kidneys, lungs, and testes were weighed at necropsy. Approximately 27 tissues were removed and examined histologically

(including reproductive organs: testes and epididymides).

GLP: Yes

Test Substance: 2-Methyl-1,5-pentanediamine, purity 99%

Results: Analytical concentrations were 9.2, 59, and 250 mg/m^3. The proportion of the test substance which was in the aerosol form was related to the total test substance concentration and was highest in the 250 mg/m^3 chamber (93%), followed by the 50 mg/m^3 chamber (89%), and lowest in the 10 mg/m^3 chamber (73%). Particle sizes were variable (4-13 microns); however, small respirable particles were present in the chambers.

Two rats in the 250 mg/m^3 group died (1 on the 8th day of exposure and 1 on the 2nd day of the recovery period). Cause of the deaths was not determined, however the deaths were attributed to test substance exposure. Red nasal and ocular discharges were observed in all groups, a clinical sign commonly seen among rats under restraint. No adverse clinical signs of toxicity were observed in the 10 or 50 mg/m^3 groups. In the 250 mg/m^3 group, clinical signs observed during the exposure phase were lung noise, irregular respiration, hunched posture, red nasal and ocular discharges, and lethargy. One rat showed slight lung noise on the 6th and 7th days of the recovery period.

The body weights of the rats in the high-dose group were significantly lower than those of controls during the exposure period and in the 1st week of the recovery period. Lung weights were increased in the 250 mg/m^3 group immediately after the 2-week exposure period and after the 2-week recovery period. No body weight or lung weight effects occurred in the 10 or 50 mg/m^3 groups.

Clinical laboratory results for rats in the 250 mg/m^3 group suggested the presence of dehydration/hemoconcentration indicated by increases in relative numbers of red blood cells, hemoglobin concentration, and hematocrit percentage, and by decreases in urine volume and increases in urine osmolality. Also, there was a decrease in lymphocytes that was considered to be a reaction to stress. There was no evidence of dehydration/hemoconcentration or lymphopenia after the 14-day recovery period.

Gross examination at necropsy showed multifocal areas of discoloration present in the lungs of the 250 mg/m^3 rats immediately after the 2-week exposure and 2-weeks later.

Microscopically, exposure-related lesions were confined to the respiratory tract and were dose-related. In the 50 and 250 mg/m^3 groups, lesions were seen in the nose, trachea, larynx/pharynx, and lung which were mainly minimal to mild in the 50 mg/m^3 group and mild to moderate in the 250 mg/m^3 group. Nasal lesions consisted of inflammation, necrosis, regeneration, and squamous metaplasia of the olfactory and respiratory epithelium; laryngeal/pharyngeal lesions consisted of subacute inflammation; tracheal lesions were hyperplasia, hypertrophy, and necrosis of the respiratory epithelium; pulmonary lesions consisted of hypertrophy and hyperplasia of bronchial and bronchiolar epithelium. After the 2-week recovery period, the above nasal and pulmonary lesions were diminished in severity, and the tracheal and laryngeal/pharyngeal lesions were no longer present. There was a slight increase in fibrous connective tissue (collagen formation) associated with pulmonary inflammatory lesions in the 250 mg/m^3 group and in 1 rat in the 50 mg/m^3 group. In the 10 mg/m^3 group, only the nose was affected. Minimal to mild inflammation of the nasal epithelium was seen in this group immediately after the 2-week exposure period. After a 2-week recovery period, the nasal lesions in this group were diminished in severity and were only seen in 2/5 rats.

A NOEL was not determined in the study, as mild microscopic changes occurred in the nasal area of rats exposed to the test substance.

Reference: DuPont Co. (1991). Unpublished Data, Haskell Laboratory Report No. 45-91, "Two-Week Inhalation Toxicity Study with Dytek® A Amine in Rats" (June 14) (also cited in TSCA Fiche OTS0555309 and OTS0571666).

Kelly, D. P. et al. (1992). The Toxicologist, 12:357 (Abstract 1399).

Reliability: High because a scientifically defensible or guideline method was used.

Additional References for Repeated Dose Toxicity: None Found.

5.3 Developmental Toxicity: No Data.

5.4 Reproductive Toxicity: No Data.

5.5 Genetic Toxicity

Type:	***In vitro* Bacterial Reverse Mutation Assay**
Tester Strain:	*Salmonella typhimurium* strains TA1535, TA97, TA98, and TA100
Exogenous Metabolic Activation:	With and without Aroclor-induced rat liver S9
Exposure Concentrations:	Without activation: 0, 10, 50, 100, 500, 1000 µg/plate With activation: 0, 50, 100, 500, 1000, 2500 µg/plate
Method:	No specific test guideline was reported; however, the mutagenicity assays were conducted using the *Salmonella* plate incorporation assay as described by Marion and Ames, 1983. A spot test in a closed system was performed to aid in identifying samples with volatile mutagenic components. Experiments without activation were performed by adding 10^8 bacteria to 2.0 mL of standard mutagenesis top agar, mixing immediately, and pouring on a Davis minimal agar plate. Experiments with activation were performed in a similar manner except that 0.5 mL of S9 mix was also added before mixing. All components used in this assay were identical to the ones used in the plate incorporation assay. A sterile disk saturated with test compound or solvent control was placed in the center of one of 2 replicate plates. The plate with the disk inverted and the replicated plate was stacked on top of it. Both plates were sealed in a plastic bag and incubated for 48 hours at 37°C. Colonies were counted on the replicate plates. The cytotoxicity of the test substance in the presence and absence of an activation system, as measured in strain TA98, was the basis for selecting concentrations for the mutagenicity experiments. The protocol used to determine cytotoxicity was identical to the mutagenicity protocol described below except that approximately 10^3 rather than 10^8 bacteria were used per plate, excess histidine was present, and no positive indicators were tested. Positive indicators (2-aminoanthracene, 2-nitrofluorene, sodium azide, and ICR-191 acridine) and negative controls

(distilled-deionized water) were included in all assays.

Treatments without activation were conducted by adding 0.1 mL of the solvent or a solution of the test substance and 0.1 mL of an overnight culture containing 10^8 bacteria to 2 mL top agar. These components were mixed and poured on the surface of a plate containing 25 mL of Davis minimal agar. Treatments with activation were conducted by adding 0.5 mL of S9 mix to the bacteria/test sample/top agar as described above and pouring the mixture onto a minimal agar plate. The S9 mix contained S9 fraction, phosphate buffered saline, and a co-factor solution. The revertant colonies were counted after the individually labeled plates were incubated at 37°C for 48 hours.

A test sample was classified as positive when: a) the number of induced revertants at 1 or more of the test sample concentrations studied was at least 2 times greater than the number of revertants in the solvent control. These dose levels must have a probability of less than 0.01 that the number of induced revertants are the same as the spontaneous revertant number; and b) a dose-response relationship is evident. A negative result was achieved when: a) the probability was greater than 0.05 that the number of revertants at each test sample concentration studied was not greater than the number of revertants in the solvent control; and b) there was no dose-response relationship. A test sample was classified as equivocal when neither of the criteria for a positive or negative was satisfied.

GLP: Yes

Test Substance: 2-Methyl-1,5-pentanediamine, purity 99.5%

Results: Negative

Remarks: The results of the spot test were negative indicating that the sample could be tested using standard toxicity and plate incorporation assays.

The test substance was toxic to strain TA98 without and with activation at 1000 and 5000 µg/plate, respectively. Based on these results, 1000 µg/plate without activation and 2500 µg/plate with activation were chosen as the highest doses for the mutagenicity assays.

There were no statistically significant increases in the number of revertants of any strain compared to solvent controls, and no linear dose-responses were detected for any treatment.

Reference:	DuPont Co. (1988). Unpublished Data, Haskell Laboratory Report No. 58-88, "Mutagenicity Testing of Dytek® A Amine in the *Salmonella typhimurium* Plate Incorporation Assay" (February 12). Marion, D. M. and B. N. Ames (1983). Mutat. Res., 113:173-215.
Reliability:	High because a scientifically defensible or guideline method was used.
Type:	***In vitro* Bacterial Reverse Mutation Assay**
Tester Strain:	*Salmonella typhimurium* strain TA1537 *Escherichia coli* WP2*uvr*A
Exogenous Metabolic Activation:	With and without Aroclor-induced rat liver S9
Exposure Concentrations:	0, 6.7, 10, 33, 67, 100, 333, 667, 1000, 3333, and 5000 µg/plate
Method:	No specific test guideline was reported; however, the experimental materials, methods, and procedures were based on those described in Ames et al., 1975; Maron and Ames, 1983; and Bridges, 1972. The study was conducted in 2 phases. The 1st phase, the initial mutagenicity assay, was used to evaluate the mutagenicity of the test substance under the conditions of the assay. The 2nd phase, the confirmatory mutagenicity assay, was used to confirm the observations of the initial assay. In the initial mutagenicity assay, the test substance was tested at 10 dose levels (maximum dose of 5000 µg/plate) along with appropriate vehicle (deionized distilled water) and positive controls (2-aminoanthracene, 2-nitrofluorene, methyl methanesulfonate, and ICR-191) in the presence and absence of rat liver microsomal enzymes. The confirmatory assay was conducted independently, using separate bacterial cultures, test article dosing solutions, and microsomal enzyme preparations than those used in the initial mutagenicity assay. The test substance was tested at the same 10 dose levels as those used in the initial mutagenicity assay, along with the appropriate vehicle and positive controls, in the presence and absence of rat liver microsomal enzymes. In the absence of S9 mix, 100 µL of tester strain and 50 µL

of vehicle, positive control, or test article were added to 2.5 mL of molten selective top agar at 45±2ºC. After vortexing to ensure homogeneity, the mixture was overlaid onto the surface of 25 mL minimal bottom agar. The plates were inverted and incubated for approximately 48 hours at 37±2ºC. Revertant colonies for a given tester strain within a given test substance dilution were counted either entirely by automated colony counter or entirely by hand. Plates with sufficient test substance precipitate to interfere with automated colony counting were counted manually. For all replicate platings, the mean number of revertants per plate were calculated and the standard deviation around the mean was also calculated.

The condition of the bacterial lawn was evaluated for evidence of test substance toxicity by using a dissecting microscope. The toxicity was scored relative to the control plate.

The top agar for *Salmonella* consisted of agar, NaCL, and L-histidine/ D-biotin. The top agar for *E. coli* consisted of agar, NaCL, and tryptophan. The bottom agar was Vogel-Bonner minimal medium E containing agar. The S9 mix contained S9 fraction, phosphate buffered saline, and a co-factor solution.

For a test substance to be evaluated positive, it must have caused a dose-related increase in the mean revertants per plate of at least 1 tester strain with a minimum of 2 increasing concentrations of test substance as specified below:

Salmonella: Data sets were judged positive if the increase in mean revertants at the peak of the dose response was equal to or greater than 3 times the mean vehicle control value.
E. coli: Data sets were judged positive if the increase in mean revertants at the peak of the dose response was equal to or greater than 2 times the mean vehicle control value.

GLP:	Yes
Test Substance:	2-Methyl-1,5-pentanediamine, purity 99.3%
Results:	Negative
Reference:	DuPont Co. (1990). Unpublished Data, Haskell Laboratory Report No. 224-90, "*Salmonella*/Mammalian-Microsome Plate Incorporation Mutagenicity Assay (Ames Test) and *Escherichia coli* WP2 *uvr*A Reverse Mutation Assay on Dytek A" (April 9).

Ames, B. N. et al. (1975). Mutat. Res., 31:347-364.

Maron, D. M. and B. N. Ames (1983). Mutat. Res., 113:173-215.

Bridges, B. A. (1972). Lab. Practice, 21:413-419.

Reliability: High because a scientifically defensible or guideline method was used.

Additional References for *In vitro* Bacterial Reverse Mutation Assay: None Found.

Type:	***In vitro* Chromosome Aberration Test**
Cell Type:	Human lymphocytes
Exogenous Metabolic Activation:	With and without Aroclor-induced rat liver S9
Exposure Concentrations:	0, 0.3, 0.6, 1.2, 2.3 mg/mL
Method:	No specific test guideline was reported; however, a scientifically defensible approach was used to conduct the study.

A study of cell proliferation kinetics, with and without S9 activation, was conducted to assess cytotoxicity.

The concurrent solvent control used in the study was distilled, deionized water. Mitomycin C and cyclophosphamide were used as positive control indicators.

Cytotoxicity Assessment: Human lymphocytes, in whole blood culture, were stimulated to divide by addition of phytohaemagglutinin. Approximately 47-54 hours after culture initiation, the medium was replaced with treatment medium. All test concentrations and solvent controls were evaluated in duplicate cultures both with and without activation. After addition of the test or control article, the cultures were incubated for approximately 3 hours at 37ºC and rinsed with Hank's Balanced Salt Solution. Five mL of fresh medium containing BrdU were then added. Incubation continued for 22 hours, with Colcemid® present during the final 2 hours to arrest the cells in metaphase. Cells were harvested and slides prepared. Slides were stained with Hoechst 33258 and Giemsa. Fifty metaphase cells per culture were scanned for replication cycles. Cell cycle delay

	and cell kinetic data were evaluated. Chromosome Aberration Test: Culture initiation, treatments, and cell harvests were conducted as described above except that: 1) BrdU was omitted from the medium, 2) test concentrations and harvest times were adjusted to 17-18 hours post-treatment, 3) positive indicators were included, and 4) 2 independent trials were performed. Slides were stained with Giemsa. For each trial, with and without activation, 100 cells (50 from each duplicate culture), were analyzed from each test level and control. Fifty cells were analyzed from 1 positive control indicator. Chromosome aberrations were tabulated and categorized as chromatid- or chromosome-type aberrations and break- or exchange-type aberrations. Chromatid and isochromatid gaps were also recorded.
GLP:	Yes
Test Substance:	2-Methyl-1,5-pentanediamine, purity 99%
Results:	Negative
Remarks:	The test substance was not cytotoxic at any concentration tested. No statistically significant increases in chromosome aberrations were observed with or without activation, nor were any concentration-related trends detected. Mitotic indices were not appreciably depressed at any concentration tested.
Reference:	DuPont Co. (1990). Unpublished Data, Haskell Laboratory Report No. 116-90, "*In vitro* Evaluation of Dytek A for Chromosome Aberrations in Human Lymphocytes" (March 16).
Reliability:	High because a scientifically defensible or guideline method was used.

Additional References for *In vitro* Clastogenicity: None Found.

Type: ***In vivo* Genetic Toxicity:** No Data.